(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 061 673**
B1

(12) # EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification: **24.10.84**

(21) Application number: **82102291.0**

(22) Date of filing: **19.03.82**

(51) Int. Cl.³: **C 07 D 217/02,**
C 07 D 401/02,
C 07 D 401/12,
C 07 D 405/02,
C 07 D 405/14,
C 07 D 413/02, C 07 D 413/12
// A61K31/47, A61K31/495,
A61K31/535

(54) **Isoquinolinesulfonyl derivatives and process for the preparation thereof.**

(30) Priority: **20.03.81 JP 39550/81**
01.06.81 JP 82559/81
12.01.82 JP 2229/82
14.01.82 JP 3291/82

(43) Date of publication of application:
06.10.82 Bulletin 82/40

(45) Publication of the grant of the patent:
24.10.84 Bulletin 84/43

(84) Designated Contracting States:
BE CH DE FR GB IT LI LU NL SE

(56) References cited:
GB-A-2 002 365
US-A-4 096 263

H. KRAUCH "Reaktionen der organischen Chemie", 5th edition, 1976 HÜTHIG VERLAG GMBH, Heidelberg page 132 "Amin-Sulfonierung"

(73) Proprietor: **Asahi Kasei Kogyo Kabushiki Kaisha**
2-6, Dojimahama 1-chome Kita-ku
Osaka-shi Osaka 530 (JP)
(73) Proprietor: **Hiroyoshi, Hidaka**
799-25, Kannonji-cho
Tsu-shi Mie-ken (JP)

(72) Inventor: **Hidaka, Hiroyoshi**
799-25, Kannonji-cho
Tsu-shi Mie-ken (JP)
Inventor: **Sone, Takanori**
131,2-4-1, Midorigaoka
Nobeoka-shi Miyazaki-ken (JP)
Inventor: **Sasaki, Yasuharu**
112, 2-4-1, Midorigaoka
Nobeoka-shi Miyazaki-ken (JP)
Inventor: **Sugihara, Taisuke**
432, 2-4-1, Midorigaoka
Nobeoka-shi Miyazaki-ken (JP)

(74) Representative: **Boeters, Hans Dietrich, Dr. et al**
Boeters, Bauer & Partner Thomas-Wimmer-Ring 14
D-8000 München 22 (DE)

Courier Press, Leamington Spa, England.

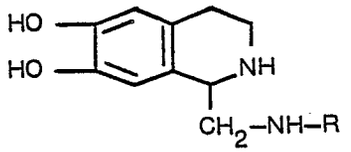
EP 0 061 673 B1

Description

BACKGROUND OF THE INVENTION

Field of the Invention

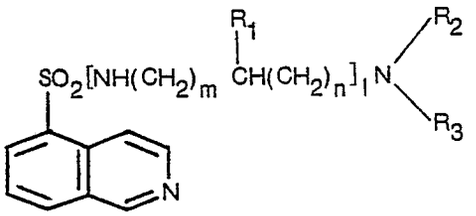
This invention relates to novel isoquinolinesulfonyl derivatives which possess a relaxatory action for vascular smooth muscle and are useful as a vasodilator and a hypotensor, and a process for the preparation thereof. US—PS 4,096,263 refers to 1,2,3,4-Tetrahydroisoquinolines of the formula



wherein R is a heterocyclic group which may have appropriate substituent(s) and pharmaceutically acceptable salts thereof together with a method for their preparation. These 1,2,3,4-Tetrahydroisoquinolines have relaxing activity on smooth muscle.

SUMMARY OF THE INVENTION

According to the present invention in one embodiment there is provided an isoquinoline derivative of Formula (I):



(I)

wherein

l is zero or one;

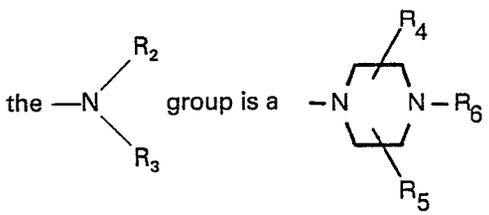
m and n each is zero or an integer of one to nine;

m+n is an integer of at least one;

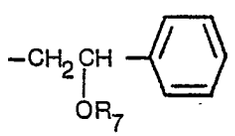
R_1 is a hydrogen atom, a C_{1-10} alkyl group or a phenyl group;

R_2 and R_3 each is a hydrogen atom, a C_{1-10} alkyl group, a C_{5-6} cycloalkyl group, a phenyl group or a benzyl group; or

R_2 and R_3 may be C_{1-6} alkylene groups and linked directly or through an oxygen atom to form a 5- to 7-membered heterocyclic ring with the adjacent nitrogen atom; or



group wherein R_4 and R_5 each is a hydrogen atom, a C_{1-10} alkyl group, a phenyl group or a benzyl or phenethyl group and R_6 is a hydrogen atom, a C_{1-10} alkyl group, a phenyl group, a benzyl or phenethyl group, a benzoyl group, a cinnamyl group, a cinnamoyl group, a furoyl group or a



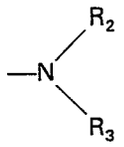
group wherein R_7 is a C_{1-10} alkyl group; and the pharmaceutically acceptable acid addition salt thereof.

The present invention in another embodiment provides a process of preparing the above described isoquinolinesulfonyl derivative.

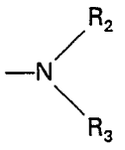
DETAILED DESCRIPTION OF THE INVENTION

Exemplary R_1 groups in Formula (I) include a hydrogen atom; C_{1-10} alkyl groups, preferably C_{1-6}

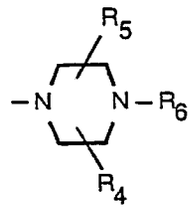
alkyl groups, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl and decyl; and phenyl groups. The R_2 and R_3 groups in Formula (I) may be the same or different and exemplary R_2 and R_3 groups include a hydrogen atom; C_{1-10} alkyl groups, preferably C_{1-6} alkyl groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl and n-decyl; C_{5-6} cycloalkyl groups such as cyclopentyl and cyclohexyl; phenyl groups; and benzyl groups. Exemplary 5- to 7-membered heterocyclic rings formed by linking R_2 and R_3 directly or through an oxygen atom together with the adjacent nitrogen atom include 1-pyrrolidinyl, piperidino, homopiperidino and morpholino groups. Preferred



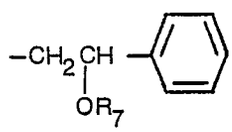
groups include amino, methylamino, ethylamino, n-propylamino, isopropylamino, n-butylamino, isobutylamino, n-hexylamino, cyclohexylamino, dimethylamino, diethylamino, di-n-butylamino, N-methyl-N-cyclopentylamino, N-methyl-N-cyclohexylamino, N-methyl-N-phenylamino, N-methyl-N-benzylamino, N-ethyl-N-benzylamino, N-isopropyl-N-benzylamino, 1-pyrrolidinyl, piperidino, homopiperidino and morpholino groups. The



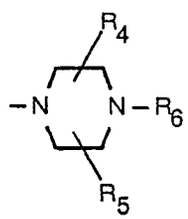
group may also be a



group. The R_2 and R_3 groups may be the same or different and exemplary R_4 and R_5 groups include a hydrogen atom; C_{1-10} alkyl groups, preferably C_{1-6} alkyl groups, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, n-pentyl, isopentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl and n-decyl; C_{5-6} cycloalkyl groups such as cyclopentyl and cyclohexyl; phenyl groups; and benzyl, α-phenethyl and β-phenethyl groups. Exemplary R_6 groups include a hydrogen atom; C_{1-10} alkyl groups, preferably C_{1-6} alkyl groups, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, n-pentyl, isopentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl and n-decyl; phenyl groups benzyl, α-phenethyl and β-phenethyl groups; a benzoyl group; a cinnamyl group; a cinnamoyl group; a furoyl group; a



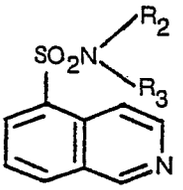
group wherein R_7 is a C_{1-8} alkyl group, preferably a C_{1-4} alkyl group, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, n-pentyl, n-hexyl, n-heptyl and n-octyl groups. Preferred



groups include piperazino, 2-methylpiperazino, 2-ethylpiperazino, 3-ethylpiperazino, 3-isopropylpiperazino, 3-isobutylpiperazino, 2-phenylpiperazino, 3-phenylpiperazino, 3-benzylpiperazino, 2,3-dimethylpiperazino, 2,5-dimethylpiperazino, 3,5-dimethylpiperazino, 2,6-dimethylpiperazino, 2-methyl-5-ethylpiperazino, 2-methyl-5-n-propylpiperazino, 2-methyl-5-isopropylpiperazino, 2-methyl-5-isobutylpiperazino, 2-methyl-5-phenylpiperazino, 2-methyl-5-benzylpiperazino, 2,5-diethylpiperazino, 2-ethyl-5-n-butylpiperazino, 4-methylpiperazino, 4-ethylpiperazino, 4-n-propylpiperazino, 4-isobutylpiperazino, 4-n-hexylpiperazino, 4-phenylpiperazino, 4-benzylpiperazino, 4-phenethylpiperazino, 4-benzoylpiperazino, 4-cinnamylpiperazino, 4-cinnamoylpiperazino, 4-furoylpiperazino, 4-(2-methoxy-2-phenethyl)piperazino and 4-(2-ethoxy-2-phenethyl)piperazino, 3-methyl-piperazino, 3,3-dimethyl-

piperazino and 4-(2-isobutoxy-2-phenethyl)-piperazino groups. Especially preferred groups are groups R_1, R_2, R_3, R_4, R_5, R_6 and R_7 mentioned in the examples. Preferred embodiments are as folows:

(a) A compound of Formula (XIII)

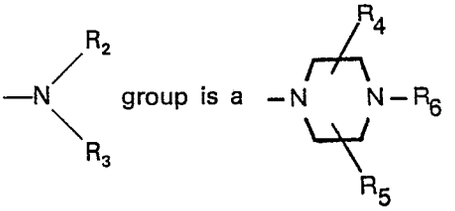


(XIII)

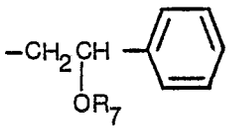
wherein

R_2 and R_3 each is a hydrogen atom, a C_{1-8} alkyl group, a phenyl group or a benzyl group, and when one of R_2 and R_3 is a hydrogen atom, the other is not a hydrogen atom; or

R_2 and R_3 are C_{1-6} alkylene groups and linked directly or through an oxygen atom to form 5- to 7-membered heterocyclic ring together with the adjacent nitrogen flow; or the



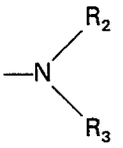
group wherein R_4 and R_5 each is a hydrogen atom, a C_{1-6} alkyl group, a phenyl group or a benzyl group and R_6 is a hydrogen atom, a C_{1-6} alkyl group, a phenyl group, a benzyl group, a phenethyl group, a benzoyl group, a cinnamyl group, a cinnamoyl group, a furoyl group or a



group wherein R_7 is a C_{1-4} alkyl group;
and pharmaceutically acceptable acid addition salts thereof, i.e., a compound of Formula (I) wherein I is zero.

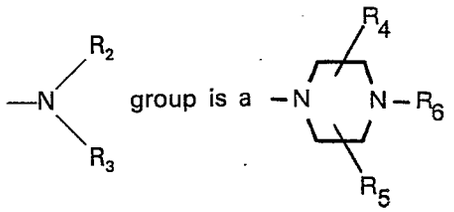
(b) The compound of (a), wherein R_2 is a hydrogen atom or a C_{1-6} alkyl group and R_3 is a C_{1-6} group.

(c) The compound of (a), wherein the



group is a 1-pyrrolidinyl group, a piperidino group or a morpholino group.

(d) The compound of (a), wherein the

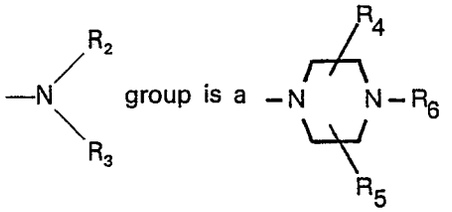


group wherein R_6 is a hydrogen atom and R_4 and R_5 each is a hydrogen atom, a C_{1-6} alkyl group, a phenyl group or a benzyl group.

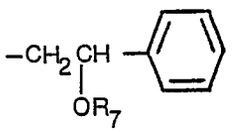
(e) The compound of (d), wherein R_6, R_4 and R_5 are hydrogen atoms.

(f) The compound of (d), wherein R_4 is a hydrogen atom or a C_{1-6} alkyl group and R_5 is a C_{1-6} alkyl group, a phenyl group or a benzyl group.

(g) The compound of (a), wherein the



group wherein R_4 and R_5 are hydrogen atoms and R_6 is a C_{1-6} alkyl group, a phenyl group, a benzyl group, a phenethyl group, a benzoyl group, a cinnamyl group, a cinnamoyl group, a furoyl group or a

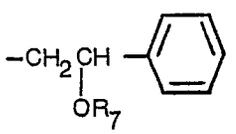


group wherein R_7 is a C_{1-4} alkyl group.

(h) The compound of (g), wherein R_6 is a C_{1-6} alkyl group.

(i) The compound of (g), wherein R_6 is a phenyl group, a benzyl group, a phenethyl group, a benzoyl group, a cinnamyl group, a cinnamoyl group or a furoyl group.

(j) The compound of (g), wherein R_6 is a



group wherein R_7 is a C_{1-4} alkyl group.

(k) A compound of Formula (XIV):

(XIV)

wherein

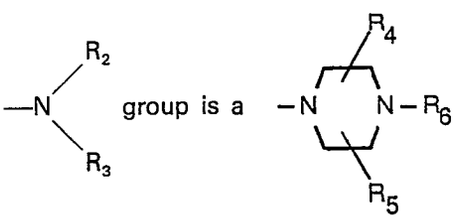
m and n each is zero or an integer of one to nine;

m+n is an integer of one to nine;

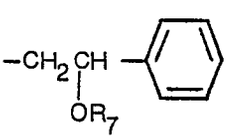
R_1 is a hydrogen atom, a C_{1-6} alkyl group or a phenyl group;

R_2 and R_3 each is a hydrogen atom, a C_{1-8} alkyl group, a C_{5-6} cycloalkyl group, a phenyl group or a benzyl group; or

R_2 and R_3 are C_{1-6} alkylene groups and linked directly or through an oxygen atom to form a 5- or 7-membered heterocyclic ring together with the adjacent nitrogen atom; or the



group wherein R_4 and R_5 each is a hydrogen atom, a C_{1-6} alkyl group, a phenyl group or a benzyl group and R_6 is a hydrogen atom, a C_{1-6} alkyl group, a phenyl group, a benzyl group, a phenethyl group, a benzoyl group, a cinnamyl group, a cinnamoyl group, a furoyl group or a



group wherein R_7 is a C_{1-4} alkyl group;
and pharmaceutically acceptable acid addition salts thereof, i.e., a compound of Formula (I), wherein I is one.

(l) The compound of (k), wherein m and n each is zero or an integer of one to nine, m+n is an integer of one to nine and R_1, R_2 and R_3 are hydrogen atoms.

(m) The compound of (k), wherein m and n each is zero or one, m+n is one, R_2 and R_3 are hydrogen atoms and R_1 is a C_{1-6} alkyl group or a phenyl group.

(n) The compound of (k), wherein m and n each is zero or an integer of one to two, m+n is one or two, R_1 is a hydrogen atom, R_2 is a hydrogen atom or a C_{1-4} alkyl group and R^3 is a C_{1-6} alkyl group, a C_{5-6} cycloalkyl group, a phenyl group or a benzyl group.

(o) The compound of (k), wherein m and n each is zero or an integer of one to two, m+n is one or two, R_1 is a hydrogen atom, R_2 is a hdyrogen atom or a C_{1-4} alkyl group and R_3 is a C_{1-6} alkyl group, a group or a morpholino group.

Exemplary isoquinolinesulfonyl derivatives of this invention include:

1) N-(2-aminoethyl)-5-isoquinolinesulfonamide referred to as "Compound (1)";
2) N-(3-amino-n-propyl)-5-isoquinolinesulfonamide referred to as "Compound (2)";
3) N-(4-amino-n-butyl)-5-isoquinolinesulfonamide referred to as "Compound (3)";
4) N-(6-amino-n-hexyl)-5-isoquinolinesulfonamide referred to as "Compound (4)";
5) N-(10-amino-n-decyl)-5-isoquinolinesulfonamide referred to as "Compound (5)";
6) N-(2-amino-1-methylethyl)-5-isoquinolinesulfonamide referred to as "Compound (6)";
7) N-(1-aminomethyl-n-propyl)-5-isoquinolinesulfonamide referred to as "Compound (7)";
8) N-(1-aminomethyl-n-pentyl)-5-isoquinolinesulfonamide referred to as "Compound (8)";
9) N-(2-amino-n-propyl)-5-isoquinolinesulfonamide referred to as "Compound (9)";
10) N-(2-amino-n-butyl)-5-isoquinolinesulfonamide referred to as "Compound (10)";
11) N-(2-amino-3-methylbutyl)-5-isoquinolinesulfonamide referred to as "Compound (11)";
12) N-(2-amino-1-phenylethyl)-5-isoquinolinesulfonamide referred to as "Compound (12)";
13) N-(2-amino-2-phenylethyl)-5-isoquinolinesulfonamide referred to as "Compound (13)";
14) N-(2-methylaminoethyl)-5-isoquinolinesulfonamide referred to as "Compound (14)";
15) N-(2-ethylaminoethyl)-5-isoquinolinesulfonamide referred to as "Compound (15)";
16) N-(2-isopropylaminoethyl)-5-isoquinolinesulfonamide referred to as "Compound (16)";
17) N-(3-dimethylamino-n-propyl)-5-isoquinolinesulfonamide referred to as "Compound (17)";
18) N-(3-diethylamino-n-propyl)-5-isoquinolinesulfonamide referred to as "Compound (18)";
19) N-(3-di-n-butylamino-n-propyl)-5-isoquinolinesulfonamide referred to as "Compound (19)";
20) N-(3-piperidino-n-propyl)-5-isoquinolinesulfonamide referred to as "Compound (20)";
21) N-(3-morpholino-n-propyl)-5-isoquinolinesulfonamide referred to as "Compound (21)";
22) N-[3-(N-methyl-N-cyclohexylamino)-n-propyl]-5-isoquinolinesulfonamide referred to as "Compound (22)";
23) N-[3-(N-methyl-N-phenylamino)-n-propyl]-5-isoquinolinesulfonamide referred to as "Compound (23)";
24) N-[3-(N-methyl-N-benzylamino)-n-propyl]-5-isoquinolinesulfonamide referred to as "Compound (24)";
25) N-methyl-5-isoquinolinesulfonamide referred to as "Compound (25)";
26) N-ethyl-5-isoquinolinesulfonamide referred to as "Compound (26)";
27) N-n-Butyl-5-isoquinolinesulfonamide referred to as "Compound (27)";
28) N-isobutyl-5-isoquinolinesulfonamide referred to as "Compound (28)";
29) N,N-dimethyl-5-isoquinolinesulfonamide referred to as "Compound (29)";
30) N,N-diethyl-5-isoquinolinesulfonamide referred to as "Compound (30)";
31) N,N-di-n-butyl-5-isoquinolinesulfonamide referred to as "Compound (31)";
32) 1-(5-isoquinolinesulfonyl)piperidine referred to as "Compound (32)";
33) 4-(5-isoquinolinesulfonyl)pyrrolidine referred to as "Compound (33)";
34) 1-(5-isoquinolinesulfonyl)morpholine referred to as "Compound (34)";
35) 1-(5-isoquinolinesulfonyl)piperazine referred to as "Compound (35)";
36) 1-(5-isoquinolinesulfonyl)-4-methylpiperazine referred to as "Compound (36)";
37) 1-(5-isoquinolinesulfonyl)-3-methylpiperazine referred to as "Compound (37)";
38) 1-(5-isoquinolinesulfonyl)-2-methylpiperazine referred to as "Compound (38)";
39) 1-(5-isoquinolinesulfonyl)-3,5-dimethylpiperazine referred to as "Compound (39)";
40) 1-(5-isoquinolinesulfonyl)-2,5-dimethylpiperazine referred to as "Compound (40)";
41) 1-(5-isoquinolinesulfonyl)-2,3-dimethylpiperazine referred to as "Compound (41)";
42) 1-(5-isoquinolinesulfonyl)-4-ethylpiperazine referred to as "Compound (42)";
43) 1-(5-isoquinolinesulfonyl)-3-ethylpiperazine referred to as "Compound (43)";
44) 1-(5-isoquinolinesulfonyl)-4-n-propylpiperazine referred to as "Compound (44)";
45) 1-(5-isoquinolinesulfonyl)-3-isopropylpiperazine referred to as "Compound (45)";
46) 1-(5-isoquinolinesulfonyl)-3-isobutylpiperazine referred to as "Compound (46)";
47) 1-(5-isoquinolinesulfonyl)-4-isobutylpiperazine referred to as "Compound (47)";
48) 1-(5-isoquinolinesulfonyl)-2,5-diethylpiperazine referred to as "Compound (48)";

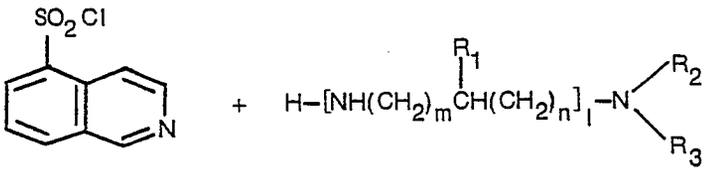
49) 1-(5-isoquinolinesulfonyl)-2-methyl-5-isobutylpiperazine referred to as "Compound (49)";
50) 1-(5-isoquinolinesulfonyl)-2-methyl-5-benzylpiperazine referred to as "Compound (50)";
51) 1-(5-isoquinolinesulfonyl)-4-n-hexylpiperazine referred to as "Compound (51)";
52) 1-(5-isoquinolinesulfonyl)-2-phenylpiperazine referred to as "Compound (52)";
53) 1-(5-isoquinolinesulfonyl)-3-phenylpiperazine referred to as "Compound (53)";
54) 1-(5-isoquinolinesulfonyl)-3-benzylpiperazine referred to as "Compound (54)";
55) 1-(5-isoquinolinesulfonyl)-4-phenylpiperazine referred to as "Compound (55)";
56) 1-(5-isoquinolinesulfonyl)-4-benzylpiperazine referred to as "Compound (56)";
57) 1-(5-isoquinolinesulfonyl)-4-β-phenethylpiperazine referred to as "Compound (57)";
58) 1-(5-isoquinolinesulfonyl)-4-benzoylpiperazine referred to as "Compound (58)";
59) 1-(5-isoquinolinesulfonyl)-4-cinnamylpiperazine referred to as "Compound (59)";
60) 1-(5-isoquinolinesulfonyl)-4-cinnamoylpiperazine referred to as "Compound (60)";
61) 1-(5-isoquinolinesulfonyl)-4-furoylpiperazine referred to as "Compound (61)";
62) 1-(5-isoquinolinesulfonyl)-4-(2-methoxy-2-phenylethyl)piperazine referred to as "Compound (62)";
63) 1-(5-isoquinolinesulfonyl)-4-(2-ethoxy-2-phenylethyl)piperazine referred to as "Compound (63)";
64) 1-(5-isoquinolinesulfonyl)-4-(2-isobutoxy-2-phenylethyl)piperazine referred to as "Compound (64)";
65) N-[2-methyl-N-benzylamino)ethyl]-5-isoquinolinesulfonamide referred to as "Compound (65)";
66) N-[2-(N-ethyl-N-benzylamino)ethyl]-5-isoquinolinesulfonamide referred to as "Compound (66)";
67) N-[2-(N-isopropyl-N-benzylamino)ethyl]-5-isoquinolinesulfonamide referred to as "Compound (67)";
68) 1-(5-isoquinolinesulfonyl)-3,3-dimethylpiperazine referred to as "Compound (68)";

and the pharmaceutically acceptable acid addition salts thereof.

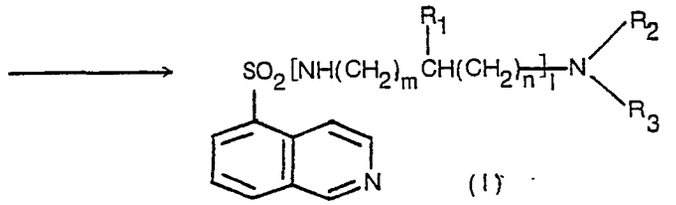
The acid addition salts of the isoquinolinesulfonyl derivatives of Formula (I) according to this invention are pharmaceutically acceptable non-toxic salts and can be prepared by conventional methods.

Suitable examples of such pharmaceutically acceptable acid addition salts include the salts of inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, and sulfuric acid; and the salts of organic acids such as acetic acid citric acid, tartaric acid, lactic acid, succinic acid, fumaric acid, maleic acid, methanesulfonic acid and p-toluenesulfonic acid.

The isoquinolinesulfonyl derivatives of Formula (I) of this invention can be prepared by reacting a 5-isoquinolinesulfonyl chloride of Formula (II) with a compound of Formula (III) in accordance with the following equation:



(II) (III)



(I)

wherein l, m, n, R_1, R_2 and R_3 are the same as defined above.

Exemplary compounds of Formula (III) include 1,2-diaminoethane, 1,3-diamino-n-propane, 1,4-diamino-n-butane, 1,5-diamino-n-pentane, 1,6-diamino-n-hexane, 1,8-diamino-n-octane, 1,10-diamino-n-decane, methylamine, ethylamine, n-propylamine, isopropylamine, n-butylamine, isobutylamine, n-hexylamine, dimethylamine, diethylamine, 2-(N-methyl-N-benzylamino)ethylamine, 2-(N-ethyl-N-benzylamino)ethylamine, 2-(N-isopropyl-N-benzylamino)ethylamine, di-n-butylamine, di-n-hexylamine, 3-(N,N-dimethylamino)-n-propylamine, 3-(N,N-diethylamino)-n-propylamine, 3-(di-n-propylamino)-n-propylamine, 3-diisopropylamino)-n-propylamine, 2-amino-n-pentylamine, 2-amino-n-propylamino, 2-amino-n-butylamine, 2-amino-3-methylbutylamine, 2-amino-1-phenylethylamine, 2-amino-2-phenylethylamine, 2-(methylamino)ethylamine, 2-(ethylamino)ethylamine, 2-(isopropyl-

amino)ethylamine, 3-(di-n-butylamino)-n-propylamine, 3-(diisobutylamino)-n-propylamine, 3-(N-methyl-N-cyclohexyl-amino)-n-propylamine, 3-(N-methyl-N-phenylamino)-n-propylamine, 3-(N-methyl-N-benzylamino)-n-propylamine, 3-(1-piperidino)-n-propylamine, 3-(1-pyrrolidino)-n-propylamine, 3-(4-morpholino)-n-propylamine, piperidine, piperazine, morpholine, pyrrolidine, 2-methylpiperazine, 1-methylpiperazine, 2-ethylpiperazine, 1-ethylpiperazine, 2-n-propylpiperazine, 1-n-propylpiperazine, 2-isopropylpiperazine, 1-isopropylpiperazine, 2-n-butylpiperazine, 1-n-butylpiperazine, 2-isobutylpiperazine, 1-isobutylpiperazine, 2-n-hexylpiperazine, 1-n-hexylpiperazine, 2,2-dimethylpiperazine, 2,3-dimethylpiperazine, 2,5-dimethylpiperazine, 2,6-dimethylpiperazine, 2,5-diethylpiperazine, 2-isobutyl-5-methylpiperazine, 2-benzyl-5-methylpiperazine, 2-phenylpiperazine, 1-phenylpiperazine, 2-benzylpiperazine, 1-benzylpiperazine, 1-phenethylpiperazine, 1-benzoylpiperazine, 1-cinnamylpiperazine, 1-cinnamoylpiperazine, 1-furoylpiperazine, 1-(2-methoxy-2-phenylethyl)-piperazine, 1-(2-ethoxy-2-phenylethyl)piperazine and 1-(2-isobutoxy-2-phenylethyl)piperazine.

The reaction between the compound of Formula (II) and the compound of the Formula (III) can be carried out in the presence or absence of an acid acceptor. Exemplary acid acceptors which can be employed include alkali metal compounds such as a hydroxide, bicarbonate, carbonate, hydride or an alkoxide, e.g. sodium bicarbonate, sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, sodium hydride and sodium alkoxides such as sodium methoxide, sodium ethoxide and sodium tert-butoxide; and organic tertiary amines such as trimethylamine, triethylamine, 1,4-diazabicyclo[2,2,2]octane and pyridine.

In general, this reaction is carried out in the presence of a reaction medium. Exemplary reaction media which can be employed include halogenated hydrocarbons such as chloroform and dichloromethane; alcohols such as methanol, ethanol and butanol; ethers such as tetrahydrofuran and dioxane; N,N-dimethylformamide, dimethyl sulfoxide, acetonitrile and water. The reaction media may be used singly or in combination with one another.

The amount of the compound of Formula (III) which can be employed is at least 1 mol and typically ranges from 1 to about 20 mols, preferably from 1 to 10 mols per mol of the compound of Formula (II). A more preferred amount of the compound of Formula (III) ranges from 1 to 5 mols per mol of the compound of Formula (II) when the acid acceptor is present, and from 2 to 10 mols per mol of the compound of Formula (II) when the acid acceptor is absent. This amount, however, does not apply to amines having a low boiling point such as methylamine and ethylamine.

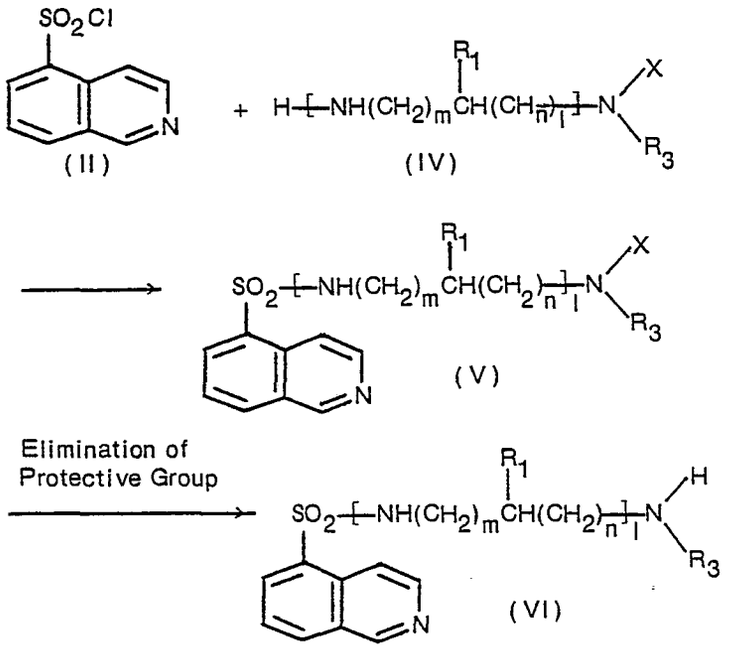
The amount of the acid acceptor employed is preferably about 0.5 to about 10 equivalents and more preferably about 1 to about 6 equivalents for each mol of the compound of Formula (III).

The reaction between the compound of Formula (II) and the compound of Formula (III) can be carried out typically at a temperature of from about −30°C to about 150°C and preferably from about 0°C to about 30°C.

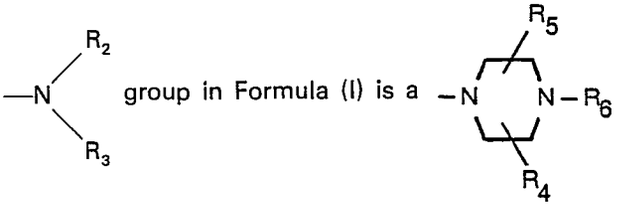
While this reaction can be carried out at a pressure above atmospheric, it is generally advisable to utilize atmospheric pressure.

The reaction time which can be employed is typically about 0.5 to about 48 hours and preferably about 0.5 to 20 hours at atmospheric pressure.

Also, when R_2 in Formula (I) is a hydrogen atom, the 5-isoquinolinesulfonyl derivatives of this invention represented by Formula (VI) can be prepared by the following equations:

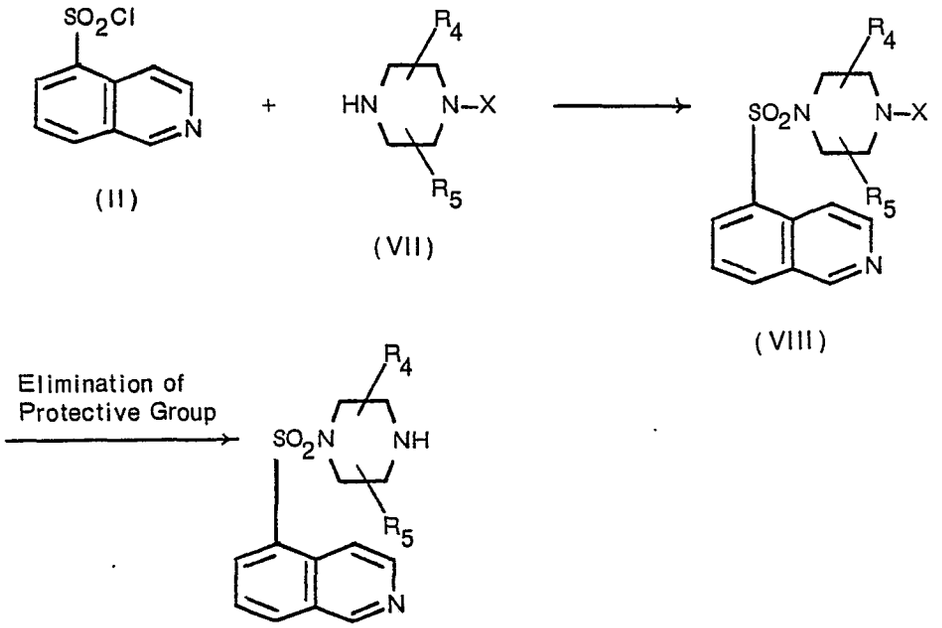


Further, when l in Formula (I) is zero, the



group in Formula (I) is a

group and R_4 is a hydrogen atom, the 5-isoquinolinesulfonyl derivatives of this invention represented by Formula (IX) can be prepared in accordance with the following equations:



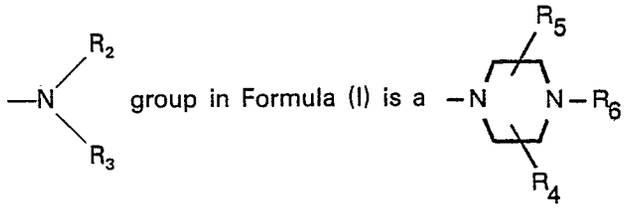
In these Formulae, l, m, n, R_1, R_3, R_4 and R_5 are the same as defined above and X is a protective group. Exemplary protective groups represented by X which can be employed in this invention include acyl groups such as formyl, acetyl and benzoyl; arylmethyloxycarbonyl groups such as benzyloxycarbonyl; alkyloxycarbonyl groups such as tert-butoxycarbonyl; and benzyl group.

Exemplary compounds of Formulae (IV) and (VII) include N^1-acetyl-1,2-diaminoethane, N^1-acetyl-1,3-diaminopropane, N^1-acetyl-1,4-diaminobutane, N^1-acetyl-1,5-diaminopentane, N^1-acetyl-1,6-diaminohexane, N^1-acetyl-1,8-diaminooctane, N^1-acetyl-1,10-diaminodecane, 2-benzyloxycarbonylamino-1-methylethylamine, 1-(benzyloxycarbonylaminomethyl)propylamine, 1-(benzyloxycarbonylaminomethyl)-pentylamine, 2-(benzyloxycarbonylamino)-propylamine, the compounds (IV) which provide the 2-amino-n-butyl group 2-(benzyloxycarbonylamino)-3-methylbutylamine, 2-acetamidopropylamine, 2-acetamido-3-methylbutylamine, 2-acetamido-2-phenylethylamine, 2-(N-benzyl-N-methylamino)ethylamine, 2-(N-benzyl-N-ethylamino)ethylamine, 2-(N-benzyl-N-isopropylamino)ethylamine, 2-(benzyloxycarbonylamino)-1-phenylethylamine, 2-(benzyloxycarbonylamino)-2-phenylethylamine, 1-formyl-3-methylpiperazine, 1-acetyl-3-methylpiperazine, 1-benzyloxycarbonyl-3-methylpiperazine, 1-t-butyloxycarbonyl-3-methylpiperazine, 1-benzyl-3-methylpiperazine, 1-benzyloxycarbonyl-3-ethylpiperazine, 1-benzyloxycarbonyl-3-phenylpiperazine and the compounds (VII) comprising the said protective group (X) providing the compounds (10), (35) to (37), (39) to (41), (43), (45) to (46), (48) to (50), (53) and (68).

The reaction between the compounds of Formula (II) and the compound of Formula (IV) and the reaction between the compound of Formula (II) and the compound of Formula (VII) can be carried out under the same reaction conditions as in the reaction between the compound of Formula (II) and the compound of Formula (III) to give the compound of Formula (V) and the compound of Formula (VIII), respectively. The method of obtaining the desired compound of Formula (VI) and the desired compound of Formula (IX) from the compound of Formula (V) and the compound of Formula (VIII), respectively, may vary depending upon the protective group of X selected, generally known methods can be employed in this invention. For example, when the protective group of X is an acyl group such as formyl

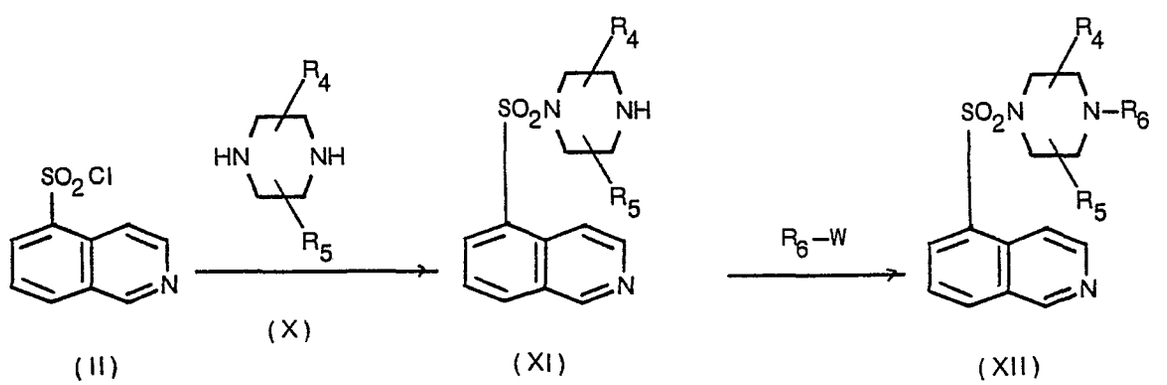
or acetyl, the desired compounds can be obtained by hydrolysis with an acid or an alkali. When the protective group of X is a benzyl group, the desired compounds can be obtained by hydrogenation. When the protective group of X is an arylmethyloxycarbonyl group such as benzyloxycarbonyl, the desired compounds can be obtained by hydrogenation or hydrolysis with an acid. When the protective group of X is an alkyloxycarbonyl group such as tert-butoxycarbonyl, the desired products can be obtained by hydrolysis with an acid.

Furthermore, when l in Formula (I) is zero, the



group in Formula (I) is a

group and R_6 is not a hydrogen atom, the 5-isoquinolinesulfonyl derivatives of this invention represented by Formula (XII) can be prepared in accordance with the following equations:



(II) (X) (XI) (XII)

In these Formulae, R_4, R_5 and R_6 are the same as defined above and W is an eliminable group. Exemplary eliminable groups include halogen atoms such as chlorine, bromine and iodine; substituted sulfonyloxy groups such as p-toluenesulfonyloxy and methanesulfonyloxy; and sulfuric acid residue. Exemplary compounds of the formula, R_6—W which can be employed include dimethyl sulfate, methyl iodide, diethyl sulfate, ethyl bromide, n-propyl iodide, n-propyl bromide, isopropyl bromide, n-butyl bromide, isobutyl bromide, n-hexyl bromide, n-hexyl-p-toluenesulfonate, benzyl chloride, benzyl bromide, phenethyl bromide, benzoyl chloride, cinnamyl chloride, cinnamoyl chloride, furoyl chloride, 2-methoxy-2-phenylethyl bromide, 2-ethoxy-2-phenylethyl bromide and 2-isobutoxy-2-phenylethyl bromide and compounds R_6—W wherein R_6 is a phenyl group.

In general, the reaction between the compound of Formula (XI) and the compound of R_6—W can be carried out in the presence of an acid acceptor. Exemplary acid acceptors which can be employed include the same ones as employed in the reaction between the compound of Formula (II) and the compound of Formula (III).

This reaction is, in general, carried out in the presence of a reaction medium. Exemplary reaction media which can be employed include the same one as employed in the reaction between the compound of Formula (II) and the compounds of Formula (III).

The amount of the compound of R_6—W which can be employed is at least 1 mol and typically ranges from 1 mol to about 20 mols, preferably from 1.2 mol to 10 mols per mol of the compound of Formula (XI).

The amount of the acid acceptor employed is preferably about 1 to about 10 equivalents and more preferably 1 to 4 equivalents for each mol of the compound of Formula (III) and (XI) respectively.

The reaction between the compound of Formula (XI) and the compound of R_6—W can be carried out typically at a temperature of from about −30°C to about 200°C and preferably from about 0°C to about 100°C.

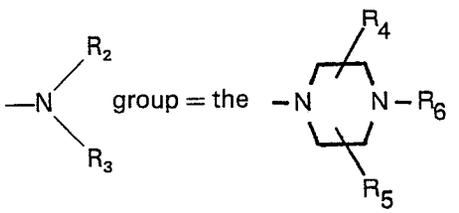
While this reaction may be carried out at a pressure above atmospheric or under reduced pressure, it is advisable to employ atmospheric pressure for practical purposes.

The method of separating and purifying the isoquinolinesulfonyl derivative of Formula (I) from the reaction solution comprises extracting the compound of Formula (I) with diluted hydrochloric acid, rendering the aqueous hydrochloric acid layer extracted basic, extracting the extract with a solvent such as chloroform capable of easily dissolving the extract, condensing the extract and subjecting the condensed residues to a silica gel column or an aluminum column chromatography for purification.

It has now been found that the isoquinolinesulfonyl derivatives of Formula (I) and the pharmaceutically acceptable salts have pharmacologically and biochemically interesting properties such as a relaxatory action for vascular smooth muscle and an action for increasing blood flow and are useful as a vasodilator, a hypotensor, an ameliorant of cerebral circulation, a medicine for angina pectoris and a preventive and a medicine for cardiovascular thrombosis.

The effect of the isoquinolinesulfonyl derivatives and the pharmaceutically acceptable acid addition salts of this invention on smooth muscle can be proved by suspending a mesenteric artery taken out from a rabbit in a helical form, contracting the mesenteric artery with potassium chloride and adding the isoquinolinesulfonyl derivatives or their pharmaceutically acceptable acid addition salts of this invention to the contracted mesenteric artery, resulting in the relaxation of the mesenteric artery. When, for example, 1-(5-isoquinolinesulfonyl)-4-methylpiperazine, i.e., Compound (36) was added and a complete relaxation was designated 100%, the concentration which could bring about a relaxation of 50%, i.e., ED_{50} was 7.7 μM, 1-(5-isoquinolinesulfonyl)piperazine, i.e., Compound (35) and N-(4-aminobutyl)-5-isoquinoline sulfonamide, i.e., Compound (3), ED_{50} were 0.6 μM and 11 μM, respectively.

The effect of the isoquinolinesulfonyl derivatives and the pharmaceutically acceptable acid addition salts of this invention on the vasodilatation of the femoral and vertebral arteries can be measured by anesthetizing a dog of mixed breed weighing 8 to 15 Kg by an intravenous administration of 35 mg/Kg of pentbarbital, providing an acute type probe (a product of Nippon Koden K.K., Japan) with the femoral and vertebral arteries, administering the isoquinolinesulfonyl derivatives and the pharmaceutically acceptable acid addition salts to the femoral vein through a polyethylene tube inserted into the femoral vein side chain and measuring the blood flow volume with an electromagnetic flowmeter (a product of Nippon Koden K.K., Japan, "MF—27"). Among the isoquinolinesulfonyl compounds of Formula (I) of this invention, those with l=0 and the



group show a high action for increasing blood flow and simultaneously a selectivity to vertebral arteries. For example, when 1 mg/Kg of 1-(5-isoquinolinesulfonyl)piperazine, i.e., Compound (35) was intravenously administered, the increased blood flow volumes in the vertebral artery and in the femoral artery were 98% and 65%, respectively. Also the isoquinolinesulfonyl compounds of Formula (I) of this invention with l=1 and one of the R_2 and R_3 groups = a hydrogen atom show a continuing blood flow increase. With 1 mg/Kg of N-(2-aminoethyl)-5-isoquinolinesulfonamide, i.e., Compound (1), an increase in the blood flow volume in the vertebral artery was continued for at least 30 minutes.

Furthermore, when the isoquinolinesulfonyl derivatives and the pharmaceutically acceptable acid addition salts of this invention are intravenously and arterially administered for the above described purposes, any remarkable toxicity cannot be observed. For example, the acute toxicity of 1-(5-isoquinolinesulfonyl)-4-methylpiperazine, i.e., Compound (36), i.e., LD_{50} was 94 mg/Kg in giving male ddY-strain mice an intravenous administration.

The following examples illustrate the present invention in more detail.

Example 1

In 200 ml of chloroform was dissolved 8.8 g of 1,4-diaminobutane, and to the solution was added dropwise 100 ml of a chloroform solution containing 4.55 g of 5-isoquinolinesulfonyl chloride under cooling with ice. After the dropwise addition of the chloroform solution, the mixed solution was stirred at a temperature of 20°C to 25°C for two hours, and then the reaction solution was extracted with a 10% aqueous hydrochloric acid solution. The pH of the aqueous layer was adjusted to 10 with a 10% aqueous sodium hydroxide solution, and the aqueous layer was extracted with chloroform. The chloroform layer extracted was washed with water and dried with anhydrous potassium carbonate. Then the chloroform was distilled from the chloroform layer, and the residue obtained was subjected to a column chromatography [silica gel: 200 g; developing solvent: 2% methanol/chloroform (volume ratio)] to give 3.46 g of N-(4-aminobutyl)-5-isoquinolinesulfonamide, i.e.; Compound (3) as an oily substance in a yield of 62%.

Mass spectrum (m/e): 279 (M^+) and 221

NMR spectrum ($CDCl_3$): 1.5—2.0 (4H, 2 x CH_2), 2.5—3.2 (4H, 2 x NCH_2), 2.4 (2H, NH_2), 7.5—7.7 (1H), 7.9—8.7 (4H) and 9.3 (1H)

IR absorption spectrum (ν_{max}^{cap}, cm^{-1}): 1330 and 1160

The same procedures as described above were repeated using the compounds of Formula (III) as set forth in Table 1—1 under the reaction conditions as set forth in Table 1—1, and N-(ω-aminoalkyl)-5-isoquinoline sulfonamides as set forth in Table 1—2 were obtained. The results and the analytical values of these compounds are shown in Table 1—2.

TABLE 1—1

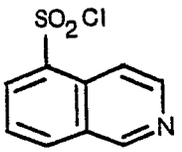
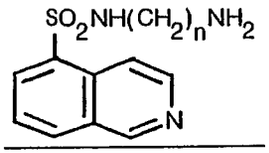
Run No.	 (g)	Compound of formula (III) (g)		Reaction Temperature (°C)	Reaction Time (hour)
1	4.55	$H_2N(CH_2)_2NH_2$	12.0	15 – 20	2
2	3.41	$H_2N(CH_2)_3NH_2$	11.1	ditto	ditto
3	4.55	$H_2N(CH_2)_6NH_2$	11.6	ditto	5
4	2.28	$H_2N(CH_2)_{10}NH_2$	8.62	ditto	10

TABLE 1-2



Run No.	Compound No.	n	Yield [g	%]	Mass Spectrum (m/e)	IR Absorption Spectrum (νSO_2, cm^{-1})	NMR Spectrum ($CDCl_3$)
1	(1)	2	3.3	(66)	222, 221 193, 129 128	3400, 1610 1330, 1165 1145, 1190 1030, 830	1.5(2H, NH_2), 2.9(4H, 2xCH_2) 7.58~7.9(1H), 8.0–8.7(4H) 9.33(1H)
2	(2)	3	2.9	(73)	265, 236 221, 143 128	3400, 1610 1350, 1330 1160, 1145 1090, 830	1.4~1.9(2H, CH_2) 2.5~3.2(4H, 2xNCH_2) 3.21(2H, NH_2), 7.62(1H) 8.0~8.8(4H), 9.33(1H)
3	(4)	6	4.6	(75)	307, 277 263, 243 221, 192 128	1590, 1320 1140, 1120 1060, 810	1.0~2.0(8H), 2.9~3.2(4H) 7.65(1H), 8.0~8.8(4H) 9.33(1H)
4	(5)	10	2.2	(61)	363, 320 292, 221 192, 128	3400, 1590 1350, 1330 1160, 1140	1.3(16H, 8xCH_2) 2.5~3.2(4H, 2xNCH_2) 3.3(2H, NH_2), 7.0(1H, NH) 7.6(1H), 8.1~8.8(4H) 9.3(1H)

Example 2

In 50 ml of dichloromethane was dissolved 1.73 g of 5-isoquinolinesulfonyl chloride, and to the solution were added 1.54 g of triethylamine and 8.0 g of monomethylamine hydrochloride. The mixture was stirred at a temperature of 10°C to 15°C for 18 hours. The reaction solution obtained was washed with water, dried with magnesium sulfate, and then the dichloromethane was distilled therefrom under reduced pressure. The residue obtained was subjected to a silica gel column chromatography (silica: 50 g; solvent: chloroform) to give 1.30 g of N-methyl-5-isoquinolinesulfonamide, i.e., Compound (25) in a yield of 77%.

Mass spectrum (m/e): 208, 148 and 128

NMR spectrum ($CDCl_3$): 2.63 (3H, singlet, NCH_3), 3.23 (1H, N*H*), 7.4—7.7 (1H), 8.1—8.7 (4H) and 9.3 (1H)

IR absorption spectrum ($\nu_{max.}^{cap}$ cm^{-1}): 3050, 2920, 1610, 1580, 1440, 1365, 1320, 1210, 1150, 1130 and 1080

The same procedures as described above were repeated using the compounds of Formula (III) as set forth in Table 2—1 under the reaction conditions as set forth in Table 2—1, and there were obtained N-ethyl-5-isoquinolinesulfonamide, i.e., Compound (26); N,N-dimethyl-5-isoquinolinesulfonamide, i.e., Compound (29); and N,N-diethyl-5-isoquinolinesulfonamide, i.e. Compound (30). The results and the analytical values of these compounds are shown in Table 2—2.

TABLE 2-1

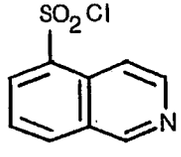
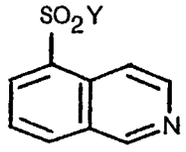
Run No.	 (g)	Compound of Formula (III) (g)		$N(C_2H_5)_3$ (g)	Reaction Temperature (°C)	Reaction Time (hour)
1	2.28	$H_2N(C_2H_5).HCl$	8.2	10	15 – 25	24
2	–ditto–	$HN(CH_3)_2.HCl$	8.2	–ditto–	–ditto–	20
3	1.50	$HN(C_2H_5)_2.HCl$	7.2	6.6	–ditto–	–ditto–

TABLE 2-2



Run No.	Compound No.	Y	Yield [g	(%)]	Mass Spectrum (m/e)	IR Absorption Spectrum cap ($\nu_{max.}$ cm^{-1})	NMR Spectrum ($CDCl_3$)
1	(26)	$-NH(C_2H_5)$	1.93	(81)	236, 164 128	3050, 2920 1600, 1560 1440, 1360 1300, 1200 1150, 1070	1.15(3H, triplet) 2.73(2H, quartet) 3.33(1H, singlet, N*H*) 7.4~7.7(1H) 8.1~8.7(4H), 9.32(1H)
2	(29)	$-N(CH_3)_2$	1.77	(75)	236, 191 143, 128	1600, 1470 1440, 1320 1145, 1125 1035, 975 940	2.85(6H, 2xCH_3) 7.5~7.9(1H) 8.2~8.5(4H), 9.3(1H)
3	(30)	$-N(C_2H_5)_2$	1.34	(77)	264, 235 191, 143	1600, 1460 1360, 1150 1120, 1050	1.2~1.4(6H, 2xCH_3) 2.2~3.3(4H, 2xNCH_2) 7.5~8.6(5H), 9.3(1H)

Example 3

In 100 ml of methylene chloride were added 6.0 g of piperazine and 1.2 g of anhydrous potassium carbonate, and to the mixture was added dropwise 30 ml of a methylene chloride solution containing 2.0 g of 5-isoquinolinesulfonyl chloride under cooling with ice. After the dropwise addition of the methylene chloride solution, the mixed solution was stirred at a temperature of 15°C to 25°C for 15 hours, and then the reaction solution was washed with water, dried with anhydrous magnesium sulfate, and the methylene chloride was distilled therefrom. The residue thus obtained was subjected to a silica gel column chromatography (silica gel: 70 g; solvent: chloroform) to give 2.14 g of 1-(5-isoquinolinesulfonyl)piperazine, i.e., Compound (35) in a yield of 89%.

Mass spectrum (m/e): 277, 234, 212, 191 and 128

NMR spectrum ($CDCl_3$): 1.65 (1H, N*H*), 2.8—3.3 (8H, 4×NCH_2), 7.5—7.9 (1H), 8.2—8.7 (4H) and 9.35 (1H)

IR absorption spectrum ($\nu_{max.}^{KBr}$ cm^{-1}): 3350, 1600, 1560, 1540, 1370 and 1160

Example 4

In 100 ml of dichloromethane was dissolved 2.28 g of 5-isoquinolinesulfonyl chloride, and to the solution were added 1.38 g of anhydrous potassium carbonate and 1.46 g of n-butylamine, and the mixture thus obtained was stirred at a temperature of 20°C to 25°C for 12 hours. The reaction solution was washed with water, dried with anhydrous magnesium sulfate, and the dichloromethane was distilled therefrom under reduced pressure. The residue thus obtained was subjected to a silica gel column chromatography (silica gel: 70 g; solvent: chloroform) to give 1.90 g of N-n-butyl-5-isoquinolinesulfonamide, i.e., Compound (27) in a yield of 72%.

Mass spectrum (m/e): 264, 211 and 191

NMR spectrum ($CDCl_3$): 0.7—1.6 (7H, C_3H_7), 2.67 (2H, NCH_2), 3.46 (1H, N*H*), 7.4—7.8 (1H), 8.1—8.6 (4H) and 9.3 (1H)

IR absorption spectrum ($\nu_{max.}^{cap}$ cm^{-1}): 3070, 2920, 1610, 1580, 1450, 1360, 1300, 1150, 1080

The same procedures as described above were repeated using the compounds of Formula (III) as set forth in Table 3—1 under the reaction conditions as set forth in Table 3—1, and there were obtained N-isobutyl-5-isoquinolinesulfonamide, i.e., Compound (28); N,N-di-n-butyl-5-isoquinolinesulfonamide, i.e., Compound (31); 1-(5-isoquinolinesulfonyl)piperidine, i.e., Compound (32); 1-(5-isoquinolinesulfonyl)pyrrolidine, i.e., Compound (33); and 1-(5-isoquinolinesulfonyl)morpholine, i.e., Compound (34). The results and the analytical values of these compounds are shown in Table 3—2.

TABLE 3-1

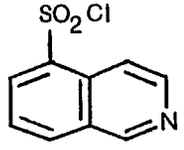
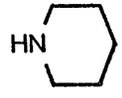
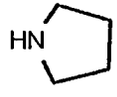
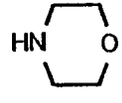
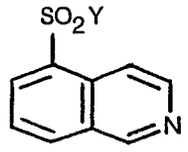
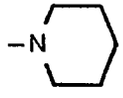
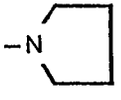
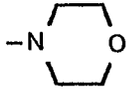
Run No.	 (g)	Compound of Formula (III) (g)		Anhydrous Potassium Carbonate (g)	Reaction Temperature (°C)	Reaction Time (hour)
1	3.0	$H_2N(i\text{-}C_4H_9)$	2.4	2.1	20 ~ 25	5
2	2.5	$HN(n\text{-}C_4H_9)_2$	3.6	1.6	-ditto-	18
3	3.0		2.8	2.1	-ditto-	12
4	-ditto-		2.5	-ditto-	-ditto-	-ditto-
5	-ditto-		2.8	-ditto-	-ditto-	-ditto-

TABLE 3-2



Run No.	Compound No.	Y	Yield [g	(%)]	Mass Spectrum (m/e)	IR Absorption Spectrum (ν cap max, cm^{-1})	NMR Spectrum ($CDCl_3$)
1	(28)	$-NH(i\text{-}C_4H_9)$	2.37	(68)	264, 211 191	3070, 2920 1610, 1580 1440, 1365 1320, 1210 1150, 1090	0.7~1.1(6H, 2xCH_3) 1.0~1.5(1H, CH) 2.55(2H, NCH_2) 3.62(1H, NH), 7.5~7.8(1H) 8.1~8.6(4H), 9.3(1H)
2	(31)	$-N(n\text{-}C_4H_9)_2$	2.43	(69)	320, 234 191, 143	1600, 1470 1360, 1150	0.9~1.9(14H, 2x$CH_2CH_2CH_3$) 2.9~3.5(4H, 2xNCH_2) 7.5~8.8(5H), 9.3(1H)
3	(32)		2.6	(71)	276, 211 191, 127	1600, 1560 1470, 1370 1150	1.4~1.9(6H, 3xCH_2) 3.0~3.3(4H, 2xNCH_2) 7.6~7.9(1H), 8.2~8.8(4H) 9.4(1H)
4	(33)		2.94	(85)	262, 211 191, 127	1600, 1550 1470, 1350 1150	1.3~1.9(4H, 2xCH_2) 3.0~3.5(4H, 2xNCH_2) 7.6~7.9(1 H) 8.2~8.8(4H), 9.3(1H)
5	(34)		2.9	(79)	278, 234 213, 191 127	1590, 1560 1540, 1470 1370, 1150	3.0~3.3(4H, 2xNCH_2) 3.6~3.8(4H, 2xOCH_2) 7.5~7.9(1H) 8.0~8.7(4H), 9.3(1H)

Example 5

In 50 ml of a chloroform solution containing 1.4 g of 3-dimethylaminopropylamine and 1.4 g of triethylamine was added dropwise 30 ml of a chloroform solution containing 2.6 g of 5-isoquinolinesulfonyl chloride under cooling with ice. After the dropwise addition of the chloroform solution, the mixed solution was stirred at a temperature of 2°C to 10°C for four hours, and the reaction mixture solution was washed with water and dried with anhydrous magnesium sulfate. After the chloroform was distilled therefrom, the residue obtained was subjected to a silica gel column chromatography (silica gel: 70 g; solvent: chloroform) to give 2.38 g of N-(3-dimethylaminopropyl)-5-isoquinolinesulfonamide, i.e., Compound (17) in a yield of 71%.

Mass spectrum (m/e): 293, 249, 235, 221 and 207

NMR spectrum ($CDCl_3$): 1.6 (2H, CH_2), 2.0—2.6 (8H, $2\times NCH_3+NCH_2$), 3.1 (2H, NCH_2), 6.2 (N*H*), 7.4—7.7 (1H), 8.0—8.6 (4H) and 9.3 (1H)

IR absorption spectrum ($\nu_{max.}^{cap}$ cm^{-1}): 2950, 2860, 2840, 1460, 1320, 1150, 1130, 830 and 760.

The same procedures as described above were repeated using the compounds of Formula (III) as set forth in Table 4—1 under the reaction conditions as set forth in Table 4—1, and there were obtained N-(3-diethylaminopropyl)-5-isoquinolinesulfonamide, i.e., Compound (18); N-(3-di-n-butylaminopropyl)-5-isoquinolinesulfonamide, i.e., Compound (19); N-(3-piperidinopropyl)-5-isoquinolinesulfonamide, i.e., Compound (20); N-(3-morpholinopropyl)-5-isoquinolinesulfonamide, i.e., Compound (21); N-[3-(N-methyl-N-cyclohexylamino)propyl]-5-isoquinolinesulfonamide, i.e., Compound (22); N-[3-methyl-N-phenylamine)propyl]-5-isoquinolinesulfonamide, i.e., Compound (23); and N-[3-(N-methyl-N-benzylamino)propyl]-5-isoquinolinesulfonamide, i.e., Compound (24). The results and the analytical values of these compounds are shown in Table 4—2.

TABLE 4-1

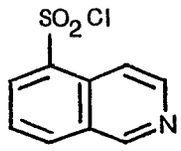
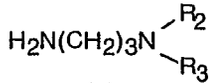
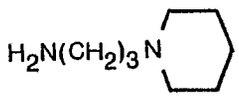
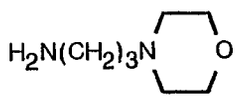
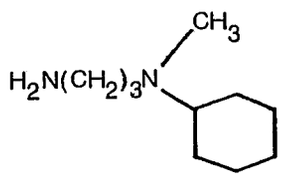
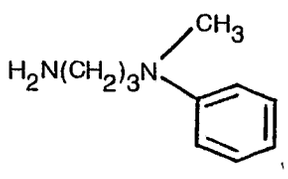
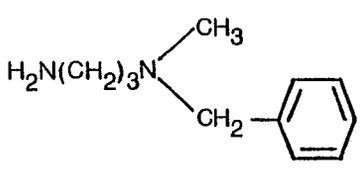
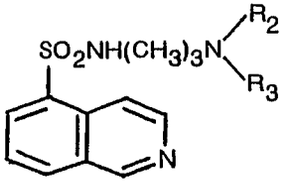
Run No.	 (g)	 (g)		$N(C_2H_5)_3$ (g)	Reaction Temperature (°C)	Reaction Time (hour)
1	1.0	$H_2N(CH_2)_3N(C_2H_5)_2$	0.7	0.67	2 ~ 5	5
2	-ditto-	$H_2N(CH_2)_3N(n\text{-}C_4H_9)_2$	1.0	-ditto-	5 ~ 10	-ditto-
3	-ditto-		0.8	-ditto-	10 ~ 20	12
4	-ditto-		0.8	-ditto-	15 ~ 25	18
5	0.44		0.4	0.3	-ditto-	-ditto-
6	-ditto-		0.38	-ditto-	-ditto-	-ditto-
7	0.75		0.75	0.5	-ditto-	-ditto-

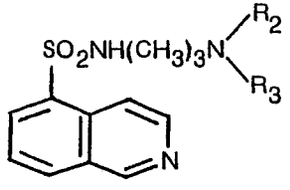
TABLE 4-2

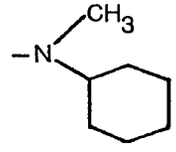
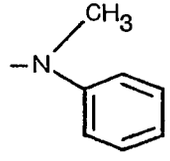
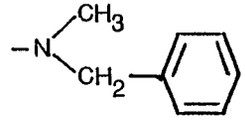


Run No.	Compound No.	$-N(R_2)(R_3)$	Yield [g	(%)]	Mass Spectrum (m/e)	IR Absorption Spectrum (ν_{max}^{cap}, cm^{-1})	NMR Spectrum ($CDCl_3$)
1	(18)	$-N(C_2H_5)(C_2H_5)$	0.75	(53)	321, 249 235, 221 207, 192	2950, 2850 1460, 1320 1160, 1130	1.1(6H, 2xCH_3) 1.5~2.0(2H, CH_2) 2.0~2.6(6H, 3xNCH_2) 3.1(2H, NCH_2), 6.8(1H, N*H*) 7.6(1H), 8.0~8.5(4H) 9.3(1H)
2	(19)	$-N(n\text{-}C_4H_9)(n\text{-}C_4H_9)$	0.93	(56)	377, 334 296, 248 234, 220 140	2960, 2870 1460, 1325 1155, 1135	0.8~2.0(16H, 2xCH_3+5xCH_2) 2.2~2.8(6H, 3xNCH_2) 3.1(2H, NCH_2), 5.4(1H, N*H*) 7.7(1H), 8.1~8.7(4H), 9.3(1H)
3	(20)	$-N$ (pyrrolidine)	0.72	(49)	332, 248 234, 220 206, 191	3075, 2920 2850, 2800 1320, 1160	1.3~2.0(8H, 4xCH_2) 2.0~2.6(6H, 3xNCH_2) 3.0(2H, NCH_2), 6.8(1H, N*H*) 7.6(1H), 8.1~8.7(4H), 9.3(1H)
4	(21)	$-N$ (morpholine)	0.63	(43)	334, 278 276, 248 234, 221 192, 143 128	2950, 2850 2820, 1320 1160, 1140 1120, 760	1.3~1.9(2H, CH_2) 2.0~2.7(6H, 3xNCH_2) 3.0(2H, NCH_2) 3.4~3.9(4H, 2xOCH_2) 6.5~7.1(1H, N*H*), 7.7(1H) 8.1~8.8(4H), 9.4(1H)

0 061 673

TABLE 4—2 (Continued)



Run No.	Compound No.	$-N(R_2)(R_3)$	Yield [g	(%)]	Mass Spectrum (m/e)	IR Absorption Spectrum (ν_{max}^{cap} cm^{-1})	NMR Spectrum ($CDCl_3$)
5	(22)		0.43	(62)	361, 318 249, 221 192, 169 126	2930, 2850 1330, 1160 1140, 790 760	0.7~1.8(12H, 6xCH_2) 2.1(3H, NCH_3) 2.1~2.8(3H, NCH_2+NCH) 2.7~3.1(2H, NCH_2) 7.1~7.5(1H, NH), 7.5(1H) 7.9~8.7(4H), 9.2(1H)
6	(23)		0.27	(39)	355, 163 134, 128 120	3050, 2900 2850, 1620 1500, 1330 1160, 1135 830, 750	1.5~1.9(2H), 2.7(3H, NCH_3) 2.8~3.4(4H, 2xNCH_2) 6.2(1H, NH), 6.5~6.8(3H) 6.9~7.3(2H), 7.6(1H) 8.0~8.6(4H), 9.25(1H)
7	(24)		0.86	(71)	369, 354 278, 221 177, 134 128, 120 91	3050, 2950 2850, 2800 1620, 1450 1330, 1210 1155, 1135	1.3~1.9(2H, CH_2), 1.95(3H, NCH_3) 2.3~2.7(2H, NCH_2) 3.0~3.3(2H, NCH_2) 3.3(2H, $C_6H_5CH_2$) 7.0~7.1(1H, NH) 7.2(5H, C_6H_5), 7.6(1H) 8.0~8.5(4H), 9.3(1H)

Example 6

In 100 ml of chloroform was dissolved 5.0 g of 1-methylpiperazine, and to the solution was added 6.9 g of anhydrous potassium carbonate. To the mixture was added dropwise 200 ml of a chloroform solution containing 1.4 g of 5-isoquinolinesulfonyl chloride under cooling with ice. After the dropwise addition of the chloroform solution, the mixed solution thus obtained was stirred for one hour under cooling with ice, and then the reaction solution was washed with 50 ml of a 5N aqueous sodium hydroxide solution and extracted twice with 50 ml of a 5N aqueous hydrochloric acid solution. The aqueous hydrochloric acid layer was rendered alkaline, extracted three times with 100 ml of chloroform, and the chloroform layer extracted was washed with water and dried with anhydrous magnesium sulfate. After the chloroform was distilled therefrom under reduced pressure, 50 ml of a 5N aqueous hydrochloric acid solution was added to the residue and the mixture was condensed to dryness under reduced pressure. The crystalline residue thus obtained was recrystallized from ethanol to give 14.9 g of 1-(5-isoquinolinesulfonyl)-4-methylpiperazine [i.e., Compound (36)] dihydrochloride in a yield of 82%.

Melting point: 215°C

Mass spectrum (m/e): 291 (M+1), 128 and 99

NMR spectrum ($CDCl_3$, δ): 2.9 (3H, s, CH_3), 3.0—4.0 (8H, m, $4\times CH_2$),7.8—8.1 (1H), 8.5—8.8 (4H) and 9.6 (1H, s)

IR absorption spectrum ($\nu_{max.}^{KBr}$ cm^{-1}): 3400, 1610, 1378, 1350, 1160 and 1140.

Example 7

In 100 ml of ethanol were added 2.77 g of 1-(5-isoquinolinesulfonyl)piperazine, i.e., Compound (35), 1.66 g of anhydrous potassium carbonate and 5.45 g of ethyl bromide, and the reaction was carried out at an external temperature of 70°C for 24 hours. After the reaction solution was filtered, the filtrate was condensed and the residue was dissolved in 50 ml of chloroform, and the solution was extracted twice with a 2N aqueous hydrochloric acid solution. The aqueous hydrochloric acid layer was rendered alkaline, extracted twice with 50 ml of chloroform, and the chloroform layer extracted was washed with water and dried with anhydrous magnesium sulfate. After the chloroform was distilled therefrom, the residue obtained was subjected to a silica gel column chromatography (silica gel: 100 g; solvent: 2% methanol-chloroform) to give 2.26 g of 1-(5-isoquinolinesulfonyl)-4-ethylpiperazine, i.e., Compound (42) in a yield of 74%.

Melting point (the dihydrochloride recrystallized from ethanol): 221°C

Mass spectrum (m/e): 305 (M^+), 290 (M—15), 277, 128 and 113

NMR spectrum ($CDCl_3$, δ): 0.9 (3H, t, CH_3), 2.2—2.8 (6H, m, $3\times CH_2$), 2.9—3.4 (4H, m, $2\times CH_2$), 7.5—8.9 (5H, m) and 9.3 (1H, s)

IR absorption spectrum ($\nu_{max.}^{cap}$ cm^{-1}): 1610, 1350, 1340 and 1140.

Example 8

The same procedures as in Example 7 were repeated except that 3.7 g of propyl bromide was employed instead of the 5.45 g of ethyl bromide. As a result there was obtained 1.53 g of 1-(5-isoquinolinesulfonyl)-4-propylpiperazine, i.e., Compound (44) in a yield of 48%.

Melting point (the dihydrochloride recrystallized from ethanol): 214°C

Mass spectrum (m/e): 319 (M^+), 290 (M—29), 127 and 88

NMR spectrum ($CDCl_3$ δ): 0.8 (3H, t, CH_3), 1.0—1.7 (2H, m, $1\times CH_2$), 2.0—2.7 (6H, m, $3\times NCH_2$), 3.0—3.3 (4H, m, $2\times NCH_2$), 7.5—8.7 (5H, m) and 9.2 (1H, s)

IR absorption spectrum ($\nu_{max.}^{cap}$ cm^{-1}): 1607, 1350, 1260, 1165 and 1140.

Example 9

In 30 ml of chloroform was added 1.42 g of 1-isobutylpiperazine and 2.76 g of potassium carbonate, and to the mixture was added dropwise 50 ml of a chloroform solution containing 2.28 g of 5-isoquinolinesulfonyl chloride under cooling with ice. After the dropwise addition of the chloroform solution, the mixed solution thus obtained was stirred at a temperature of 15°C to 25°C for two hours, and then the reaction solution was washed with 20 ml of a 1N aqueous sodium hydroxide solution and extracted twice with a 5N aqueous hydrochloric acid solution. The aqueous hydrochloric acid layer was rendered alkaline, extracted three time with 30 ml of chloroform, and the chloroform layer extracted was washed with water and dried with anhydrous magnesium sulfate. After the chloroform was distilled therefrom under reduced pressure, the residue obtained was subjected to a silica gel column chromatography (silica gel: 100 g; solvent: 2% methanol-chloroform) to give 2.60 g of 1-(5-isoquinolinesulfonyl)-4-isobutylpiperazine, i.e., Compound (47) in a yield of 78%.

Melting point (the dihydrochloride recrystallized from ethanol): 234°C

Mass spectrum (m/e): 333 (M^+), 290 ($M-C_3H_7$), 141 and 128

NMR spectrum ($CDCl_3$, δ): 0.8 (6H, d, $2\times CH_3$), 1.2—2.0 (1H, m, CH), 2.0—3.3 (10H, $5\times NCH_2$), 7.6—8.8 (5H) and 9.3 (1H, s)

IR absorption spectrum ($\nu_{max.}^{cap}$ cm^{-1}): 3430, 1620, 1350, 1340, 1170 and 1145.

The same procedures as described above were repeated using the compounds of Formula (III) as set forth in Table 5—1 under the reaction conditions as set forth in Table 5—1, and there were obtained 1-(5-isoquinolinesulfonyl)-4-n-hexylpiperazine, i.e., Compound (51); 1-(5-isoquinolinesulfonyl)-phenylpiperazine, i.e., Compound (55); 1-(5-isoquinolinesulfonyl)-4-phenethylpiperazine, i.e., Compound (57); 1-(5-isoquinolinesulfonyl)-4-cinnamylpiperazine' i.e., Compound (59); and 1-(5-isoquinolinesulfonyl)-4-(2-ethoxy-4-phenylethyl)piperazine, i.e., Compound (63). The results and the analytical values of these compounds are shown in Table 5—2.

TABLE 5-1

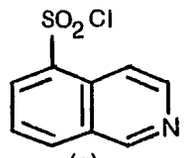
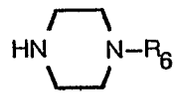
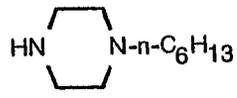
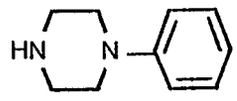
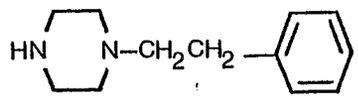
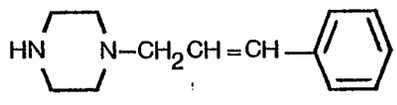
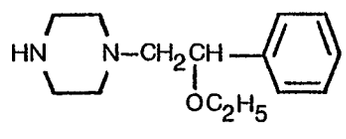
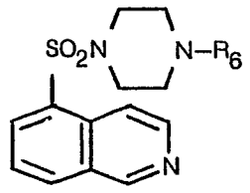
Run No.	 (g)	 (g)		K_2CO_3 (g)	Reaction Temperature (°C)	Reaction Time (hour)
1	2.28		1.70	2.76	15 ~ 25	2
2	-ditto-		1.62	-ditto-	-ditto-	-ditto-
3	-ditto-		1.9	-ditto-	-ditto-	-ditto-
4	-ditto-		2.1	-ditto-	-ditto-	-ditto-
5	-ditto-		2.34	-ditto-	-ditto-	-ditto-

TABLE 5-2



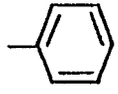
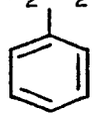
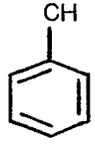
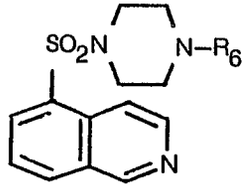
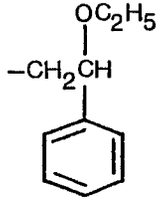
Run No.	Compound No.	R_6	Yield [g	(%)]	Mass Spectrum (m/e)	IR Absorption Spectrum (ν cap max, cm^{-1})	NMR Spectrum ($CDCl_3$)
1	(51)	n-C_6H_{13}	2.64	(73)	361, 290 169, 98	1620, 1460 1350, 1335 1170, 1140	0.6~1.8(11H, 4xCH_2+CH_3) 3.2~3.7(6H, 3xNCH_2) 3.1~3.5(4H, 2xNCH_2) 7.4~8.8(5H), 9.3(1H)
2	(55)		2.44	(69)	353, 278 161	3400, 1605 1360, 1170 1150	3.8(8H, 4xNCH_2) 7.6(5H, C_6H_5) 7.6~9.0(5H), 9.2(1H)
3	(57)	$-CH_2CH_2$ 	2.44	(64)	290 (M–$CH_2C_6H_5$)	3400, 1350 1330, 1155 950	2.5~4.0(12H, 6xCH_2) 7.3(5H), 7.9~9.0(5H) 9.8(1H) (d^6-dimethyl sulfoxide)
4	(59)	$-CH_2CH$ CH 	3.58	(91)	394, 303 202, 117	3400, 1350 1165, 1140 935	4.0(8H, 4xNCH_2) 3.9(2H, NCH_2CH=) 6.0~6.5(1H), 6.9(1H) 7.3~7.5(5H), 8.0~9.2(5H) 9.9(1H) (CD_3OD)

TABLE 5-2 (Continued)



Run No.	Compound No.	R_6	Yield [g	(%)]	Mass Spectrum (m/e)	IR Absorption Spectrum (ν cap max, cm^{-1})	NMR Spectrum ($CDCl_3$)
5	(63)		3.9	(92)	381(M-44) 290	3400, 1340 1160, 1135	1.2(3H, CH_3) 2.5~4.5(13H, 6xCH_2+CH) 7.2(5H), 7.5~9.0(5H) 9.3(1H)

Example 10

In 150 ml of ethanol were added 2.77 g of 1-(5-isoquinolinesulfonyl)piperazine, i.e., Compound (35), 1.0 g of potassium hydroxide and 1.9 g of benzyl chloride, and the mixture was refluxed under heating for five hours. After the ethanol was removed from the reaction solution, 100 ml of chloroform was added to the resulting solution, and the solution obtained was washed with a buffer solution having a pH of 5.5 and extracted twice with 20 ml of a 2N aqueous hydrochloric acid solution. The aqueous hydrochloric acid layer was rendered alkaline, extracted twice with 50 ml of chloroform, and the chloroform layer extracted was washed with water and dried with anhydrous magnesium sulfate. After the chloroform was distilled therefrom under reduced pressure, 5 ml of a 10N aqueous hydrochloric acid solution was added to the residue and the mixture was condensed to dryness. The crystalline residue thus obtained was recrystallized from ethanol to give 2.9 g of 1-(5-isoquinolinesulfonyl)-4-benzylpiperazine [i.e., Compound (56)] dihydrochloride in a yield of 66%.

Melting point: 230°C

Mass spectrum (m/e): 361 (M+1), 290 (M—C_5H_{11}), 169 and 98

NMR spectrum (d^6-dimethyl sulfoxide, δ): 3.0—4.0 (8H, 4×NCH_2), 3.3 (2H, s, NCH_2), 7.8—8.8 (5H) and 9.3 (1H, s)

IR absorption spectrum ($\nu_{max.}^{KBr}$ cm^{-1}): 3350, 3450, 1360 and 1165.

Example 11

In 50 ml of chloroform were added 2.77 g of 1-(5-isoquinolinesulfonyl)piperazine, i.e., Compound 35 and 1.54 g of anhydrous potassium carbonate, and to the mixture was added dropwise 1.70 g of benzoyl chloride under cooling with ice, and the mixture was stirred at a temperature of 15°C to 20°C for three hours. The reaction solution was washed with a 1N aqueous sodium hydroxide solution, then with water and dried with anhydrous magnesium sulfate. After the chloroform was distilled therefrom, the residue thus obtained was subjected to a silica gel column chromatography (silica gel: 70 g; solvent: chloroform) to give 2.7 g of 1-(5-isoquinolinesulfonyl)-4-benzoylpiperazine, i.e., Compound (58) in a yield of 71%.

Melting point (the hydrochloride): 217°C

Mass spectrum (m/e): 381 (M^+), 318, 276 and 289

NMR spectrum ($CDCl_3$, δ): 3.1—3.9 (8H, 4×CH_2), 7.2 (5H), 7.5—8.5 (5H) and 9.3 (1H)

IR absorption spectrum ($\nu_{max.}^{cap}$ cm^{-1}): 1690, 1370 and 1160.

The same procedures as described above were repeated using the compounds of the formula, R_6—W under the reaction conditions as set forth in Table 6—1, and there were obtained 1-(5-isoquinolinesulfonyl)-4-cinnamoylpiperazine, i.e., Compound (60) and 1-(5-isoquinolinesulfonyl)-4-furoylpiperazine, i.e., Compound (61). The results and the analytical values of these compounds are shown in Table 6—2.

TABLE 6-1

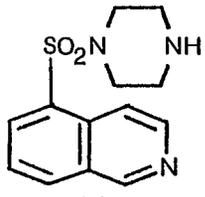
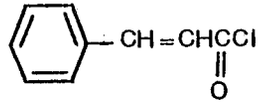
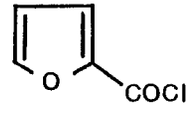
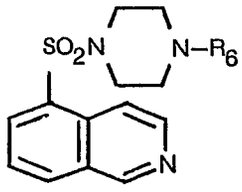
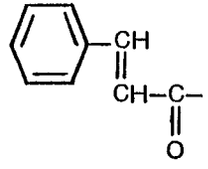
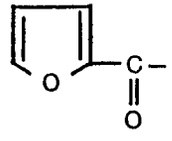
Run No.	 (g)	R_6–W (g)		K_2CO_3 (g)	Reaction Temperature (°C)	Reaction Time (hour)
1	2.77		2.0	1.54	15 ~ 20	3
2	–ditto–		1.58	–ditto–	–ditto–	–ditto–

TABLE 6-2



Run No.	Compound No.	R_6	Yield [g	(%)]	Mass Spectrum (m/e)	IR Absorption Spectrum (ν cap max, cm^{-1})	NMR Spectrum ($CDCl_3$)
1	60		3.26	(80)	407, 344 277, 215	3400, 1645 1600, 1360 1165	3.2~3.8(8H, 4xCH_2) 6.7~7.5(2H, 2xCH) 7.3(5H), 7.9~9.2(5H) 10.0(1H)
2	61		3.26	(88)	371	3400, 1620 1490, 1335 1170, 1150	3.0~4.0(8H, 4xCH_2) 6.4(1H), 6.95(1H) 7.4(1H), 7.4~8.8(5H) 9.3(1H)

Example 12

In 30 ml of methylene chloride were dissolved 1.75 g of 2,5-dimethylpiperazine and 1.53 g of triethylamine, and to the solution was added dropwise 20 ml of a methylene chloride solution containing 1.73 g of 5-isoquinolinesulfonyl chloride under cooling with ice. After the dropwise addition of the methylene chloride solution, the mixed solution obtained was stirred at a temperature of 5°C to 10°C for three hours, and then the reaction mixture solution was washed with water and dried with anhydrous magnesium sulfate. After the methylene chloride was distilled therefrom, the residue obtained was subjected to an alumina column chromatography (alumina: 50 g; solvent: chloroform) to give 1.38 g of 1-(5-isoquinolinesulfonyl)-2,5-dimethylpiperazine, Compound (40) in a yield of 59%.

Mass spectrum (m/e): 305, 277, 249, 192 and 128

NMR spectrum ($CDCl_3$): 0.8—1.3 (6H, $2\times CH_3$), 1.7 (1H, N*H*), 2.3—4.2 (6H, $2\times CH_2+2\times CH$), 7.6 (1H), 8.0—8.8 (4H) and 9.3 (1H).

The same procedures as described above were repeated using the compounds of Formula (III) as set forth in Table 7—1 under the reaction conditions as set forth in Table 7—1, and there were obtained 1-(5-isoquinolinesulfonyl)-3-methylpiperazine, i.e., Compound (37); 1-(5-isoquinolinesulfonyl)-3,5-dimethylpiperazine, i.e., Compound (39); 1-(5-isoquinolinesulfonyl)-2,3-dimethylpiperazine, i.e., Compound (41); 1-(5-isoquinolinesulfonyl)-3-ethylpiperazine, i.e., Compound (43); 1-(5-isoquinolinesulfonyl)-3-isopropylpiperazine, i.e., Compound (45); 1-(5-isoquinolinesulfonyl)-3-isobutylpiperazine, i.e., Compound (46); 1-(5-isoquinolinesulfonyl)-2,5-diethylpiperazine, i.e., Compound (48); 1-(5-isoquinolinesulfonyl)-2-methyl-5-isobutylpiperazine, i.e., Compound (49); 1-(5-isoquinolinesulfonyl)-2-methyl-5-benzylpiperazine, i.e., Compound (50); 1-(5-isoquinolinesulfonyl)-3-phenylpiperazine, i.e., Compound (53); 1-(5-isoquinolinesulfonyl)-3-benzylpiperazine, i.e., Compound (54); and 1-(5-isoquinolinesulfonyl)-3,3-dimethylpiperazine, i.e., Compound (68).

The results and the analytical values of these compounds are shown in Table 7—2.

TABLE 7-1

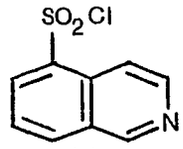
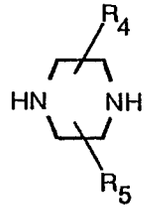
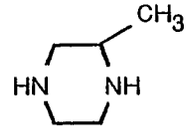
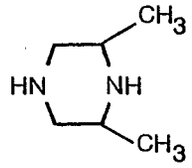
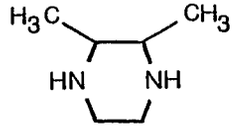
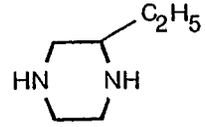
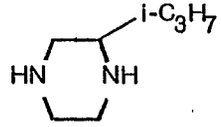
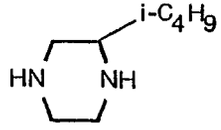
Run No.	 (g)	 (g)		$N(C_2H_5)_3$ (g)	Reaction Temperature (°C)	Reaction Time (hour)
1	1.73		1.52	1.53	2 ~ 10	2
2	–ditto–		1.73	–ditto–	–ditto–	–ditto–
3	1.0		1.25	1.1	15 ~ 25	1
4	1.14		1.14	1.0	–ditto–	10
5	–ditto–		1.28	–ditto–	–ditto–	18
6	–ditto–		1.42	–ditto–	–ditto–	–ditto–

TABLE 7-1 (Continued)

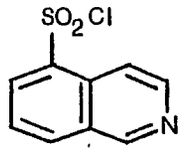
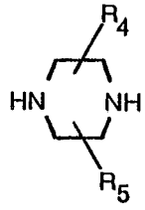
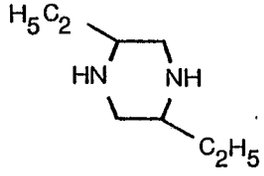
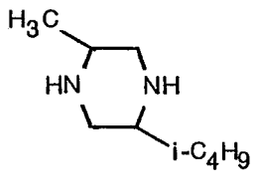
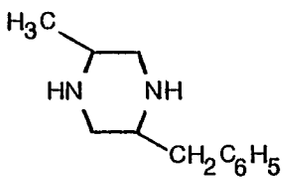
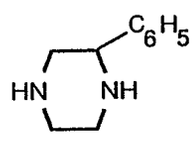
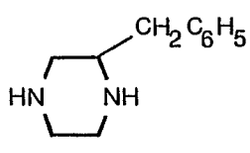
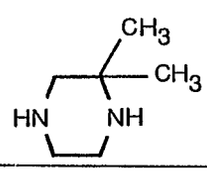
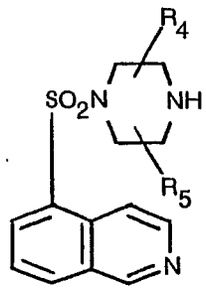
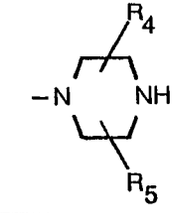
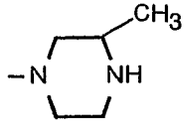
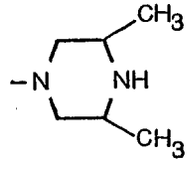
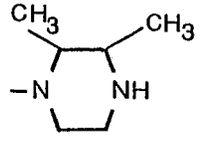
Run No.	 (g)	 (g)		$N(C_2H_5)_3$ (g)	Reaction Temperature (°C)	Reaction Time (hour)
7	1.73		2.28	1.53	15 ~ 25	18
8	1.0		3.43	2.3	38	20
9	-ditto-		4.17	-ditto-	-ditto-	-ditto-
10	-ditto-		3.56	-ditto-	-ditto-	-ditto-
11	-ditto-		3.90	-ditto-	-ditto-	-ditto-
12	1.14		1.14	1.0	15 ~ 25	-ditto-

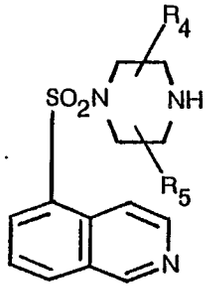
TABLE 7-2

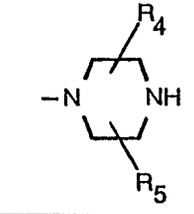
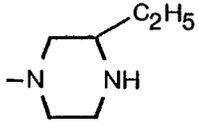
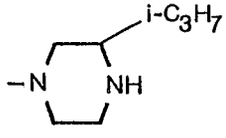
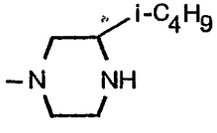
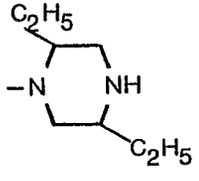


Run No.	Compound No.		Yield [g	(%)]	Mass Spectrum (m/e)	IR Absorption Spectrum (ν cap max, cm^{-1})	NMR Spectrum ($CDCl_3$)
1	(37)		1.60	(88)	276, 206 162, 148	3300, 3000 2950, 2850 1610, 1560 1480, 1360 1330, 1160 1140, 1070 1040	0.95(3H, C*H*$_3$), 1.6(1H, N*H*) 1.8~3.2(5H), 3.65(2H) 7.6(1H), 8.1~8.7(4H) 9.3(1H)
2	(39)		2.14	(92)	305, 278 264, 249 192, 128 114	3350, 2920 2850, 1450 1370, 1330 1155, 1140	1.0(6H, 2xC*H*$_3$), 2.1(2H) 2.5~3.3(2H), 3.6~4.0(2H) 4.3(1H, N*H*), 7.8(1H) 8.1~8.8(4H), 9.4(1H)
3	(41)		1.0	(75)	305, 277 249, 192 128	3400, 2920 2850, 1610 1360, 1330 1160, 1140	0.9~1.3(6H, 2xC*H*$_3$) 1.6(1H, N*H*), 2.6~4.3(6H) 7.6(1H), 8.1~8.8(4H) 9.3(1H)

0 061 673

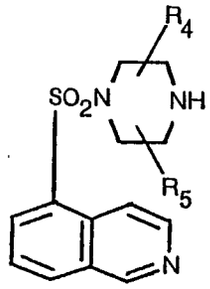
TABLE 7-2 (Continued)



Run No.	Compound No.		Yield [g (%)]	Mass Spectrum (m/e)	IR Absorption Spectrum (ν_{max}^{cap} cm^{-1})	NMR Spectrum ($CDCl_3$)
4	(43)		1.07 (70)	305, 206 192, 128 114	3400, 2950 2800, 1600 1360, 1340 1160, 1140	1.0(3H, C*H*$_3$), 1.4(2H) 2.1(1H, N*H*), 1.8~3.0(5H) 3.6(2H), 7.6(1H) 8.0~8.6(4H), 9.3(1H)
5	(45)		1.02 (64)	319, 276 221, 128	3400, 1610 1480, 1370 1335, 1160 1130	0.7~1.3(7H, C$_3$*H*$_7$), 2.1(1H, N*H*) 1.8~3.5(5H), 3.7(2H) 7.6(1H), 8.1~8.8(4H) 9.3(1H)
6	(46)		1.07 (64)	333, 221 128	3350, 1600 1470, 1360 1330, 1160 1140	0.5~1.3(9H, C$_4$*H*$_9$), 2.7(1H, N*H*) 2.0~3.4(5H), 3.75(2H) 7.5(1H), 8.1~8.7(4H), 9.3(1H)
7	(48)		1.65 (65)	333, 265 248, 192	3400, 1610 1400, 1360 1340, 1160 1130	0.7~1.8(10H, 2xC$_2$*H*$_5$), 1.7(1H) 2.3~4.3(6H), 7.6(1H) 8.0~8.7(4H), 9.3(1H)

0 061 673

TABLE 7-2 (Continued)



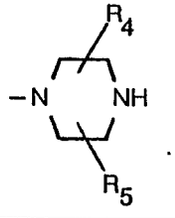
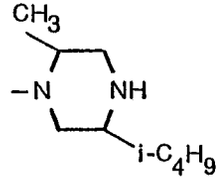
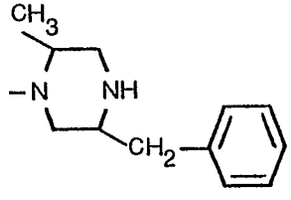
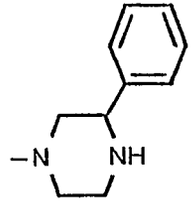
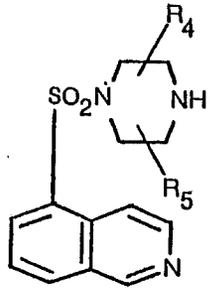
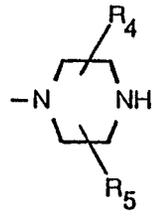
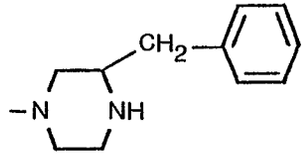
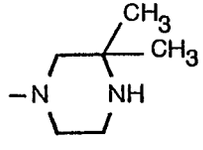
Run No.	Compound No.		Yield [g (%)]	Mass Spectrum (m/e)	IR Absorption Spectrum (ν_{max}^{cap}, cm^{-1})	NMR Spectrum ($CDCl_3$)
8	(49)		0.88 (58)	347, 220 192, 128	3400, 1610 1450, 1360 1340, 1160 1130	0.7 ~ 1.8(12H, C_4H_9+CH_3) 1.8(1H), 2.0 ~4.1(6H), 7.7(1H) 8.1 ~ 8.8(4H), 9.3(1H)
9	(50)		1.25 (75)	381, 291 220, 128	3350, 1600 1500, 1355 1340, 1160 1130	1.0(3H, CH_3), 1.6(1H, N*H*) 2.0~ 4.3(8H), 7.1(5H) 7.6(1H), 8.0~ 8.6(4H) 9.3(1H)
10	(53)		1.23 (79)	353, 312 278, 235 192, 167	3300, 1600 1510, 1360 1335, 1160 1140	1.6(1H), 1.8~3.2(5H) 3.65(2H), 7.2(5H) 7.6(1H) 8.1~8.7(4H) 9.3(1H)

TABLE 7-2 (Continued)

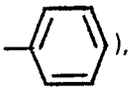


Run No.	Compound No.		[g	Yield (%)]	Mass Spectrum (m/e)	IR Absorption Spectrum (ν cap max, cm^{-1})	NMR Spectrum ($CDCl_3$)
11	(54)		1.13	(70)	367, 276 220, 148 128	3400, 1600 1500, 1360 1340, 1160 1140	1.0 ~ 1.5(2H), 1.9(1H) 1.9 ~ 3.2(5H), 3.7(2H) 7.2(5H), 7.6(1H) 8.1 ~ 8.7(4H), 9.3(1H)
12	(68)		0.96	(63)	305, 290 276, 191 129	3300, 3000 2950, 1620 1560, 1370 1160, 1140	1.2(6H, 2xCH_3), 1.3 ~ 2.1(1H, N*H*) 2.6 ~ 3.4(6H, 3xCH_3), 7.6(1H) 8.0 ~ 8.7(4H), 9.3(1H)

0 061 673

Example 13

In 50 ml of chloroform were dissolved 4.68 g of 1-benzyloxycarbonyl-3-methylpiperazine and 1.01 g of triethylamine, and to the solution was added dropwise 20 ml of a chloroform solution containing 4.55 g of 5-isoquinolinesulfonyl chloride, and the mixed solution was stirred at a temperature of 20°C to 25°C for 20 hours. The reaction solution obtained was washed with a saturated aqueous sodium hydrogencarbonate solution then with a saturated aqueous ammonium chloride solution, dried with anhydrous magnesium sulfate and concentrated to dryness under reduced pressure to 8.1 g of 1-(5-isoquinolinesulfonyl)-4-benzyloxycarbonyl-2-methylpiperazine as a yellowish white oily substance.

NMR spectrum ($CDCl_3$): 1.0 (3H, d, CH_3), 2.5—4.3 (7H), 5.0 (2H, S, OCH_2— ), 7.25 (5H, S, C_6H_5), 7.55 (1H), 8.0—8.7 (4H) and 9.2 (1H)

IR absorption spectrum ($\nu_{max.}^{cap}$, cm^{-1}): 1700, 1360 and 1130.

To 1.65 g of 1-(5-isoquinolinesulfonyl)-4-benzyloxycarbonyl-2-methylpiperazine as obtained above was added 5 ml of 25% hydrobromic acid-acetic acid, and the mixture was stirred at 20°C for five hours. To the reaction solution was added 30 ml of ethyl ether, and the crystals precipitated were separated by filtration. The crystals thus obtained were dissolved in 20 ml of water and washed with chloroform. Then the pH of the aqueous layer was adjusted to 9 with a 1N aqueous sodium hydroxide solution, extracted with chloroform, and the chloroform layer was washed with water and dried with anhydrous magnesium sulfate. Then the chloroform was distilled therefrom under reduced pressure to give 1.05 g of 1-(5-isoquinolinesulfonyl)-2-methylpiperazine, i.e., Compound (38) in a yield of 93%.

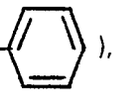
Mass spectrum (m/e): 291, 277, 249, 192, 129 and 128

NMR spectrum ($CDCl_3$): 1.3 (6H, d, $2\times CH_3$), 1.9 (1H, N*H*), 2.2—3.1 (4H), 3.1—4.0 (2H), 4.2 (1H), 7.7 (1H), 8.1—8.8 (4H) and 9.3 (1H)

IR absorption spectrum ($\nu_{max.}^{cap}$, cm^{-1}): 3330, 2940, 2870, 2830, 1607, 1370, 1320, 1160, 1135, 990 and 760

Example 14

In 40 ml of chloroform were dissolved 2.23 g of 2-benzyloxycarbonyl-1-methylethylamine and 1.2 g of triethylamine, and to the solution was added dropwise 20 ml of a chloroform solution containing 2.28 g of 5-isoquinolinesulfonyl chloride under cooling with ice. After the dropwise addition of the chloroform solution, the mixed solution was stirred at a temperature of 20°C to 25°C for two hours. The reaction solution obtained was washed with a saturated aqueous hydrogencarbonate solution, then with water, dried with anhydrous magnesium sulfate and then the chloroform was distilled therefrom under reduced pressure to give 3.55 g of N-(2-benzyloxycarbonylamino-1-methylethyl)-5-isoquinolinesulfonamide in a yield of 89%.

NMR spectrum ($CDCl_3$): 0.95 (3H, CH_3), 2.5—4.5 (3H), 5.0 (2H, OCH_2— ), 6.6 (1H), 7.2 (5H), 7.6 (1H), 8.0—8.6 (4H) and 9.3 (1H)

IR absorption spectrum ($\nu_{max.}^{cap}$, cm^{-1}): 3350, 1700, 1330 and 1160.

To 2.0 g of N-(2-benzyloxycarbonylamino-1-methylethyl)-5-isoquinolinesulfonamide as obtained above was added 5 ml of 25% hydrobromic acid-acetic acid, and the mixture was stirred at a temperature of 20°C to 25°C for 20 hours. To the reaction solution was added 30 ml of ethyl ether, and the crystals precipitated were separated by filtration. The crystals thus obtained were dissolved in 20 ml of water, washed with chloroform, rendered alkaline with a 1N sodium hydroxide solution and extracted with chloroform. The chloroform layer was washed with water, dried with anhydrous magnesium sulfate and the chloroform was distilled under reduced pressure to give 1.2 g of N-(2-amino-1-methylethyl)-5-isoquinolinesulfonamide, i.e., Compound (6) in a yield of 90%.

Mass spectrum (m/e): 265, 240, 221, 192 and 128

NMR spectrum ($CDCl_3$): 1.1 (3H), 1.7 (2H), 2.6 (2H), 3.7 (1H), 6.5 (1H), 7.6 (1H), 8.0—8.7 (4H) and 9.3 (1H)

IR absorption spectrum ($\nu_{max.}^{cap}$, cm^{-1}): 3400, 2900, 1610, 1460, 1330, 1160 and 1140.

The same procedures as described above were repeated using the compounds of Formula (III) as set forth in Table 8—1 under the reaction conditions as set forth in Table 8—1 and Table 8—2, and there were obtained N-(1-aminomethylpropyl)-5-isoquinolinesulfonamide, i.e., Compound (7); N-(1-aminomethylpentyl)-5-isoquinolinesulfonamide, i.e., Compound (8); and N-(2-amino-1-phenylethyl)-5-isoquinolinesulfonamide, i.e., Compound (12). The analytical values of these compounds thus obtained are shown in Table 8—3.

TABLE 8-1

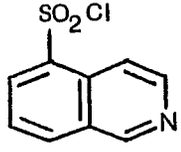
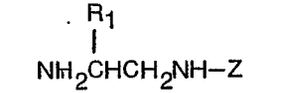
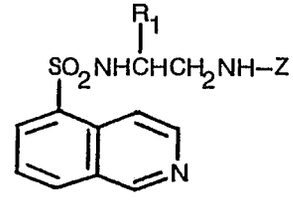
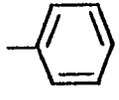
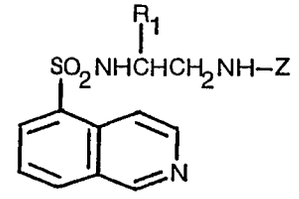
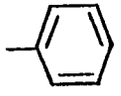
Run No.	 (g)	 R_1	(g)	$N(C_2H_5)_3$ (g)	Reaction Temperature (°C)	Reaction Time (hour)	 Yield [g	(%)]	IR Absorption Spectrum cap (ν max, cm^{-1})
1-1	2.28	C_2H_5	2.4	1.2	20 ~ 25	4	3.5	(85)	1710, 1330, 1160
2-1	-ditto-	$n\text{-}C_4H_9$	2.8	-ditto-	-ditto-	-ditto-	3.1	(70)	1710, 1340, 1160
3-1	-ditto-		3.0	-ditto-	-ditto-	-ditto-	3.4	(74)	1710, 1330, 1160

TABLE 8-2



Run No.	R_1	(g)	25% HBr–CH_3COOH (ml)	Reaction Temperature (°C)	Reaction Time (hour)	Product Compound No.	Yield [g	(%)]
1–2	C_2H_5	1.5	5	20 ~ 25	12	(7)	0.90	(89)
2–2	n-C_4H_9	–ditto–	–ditto–	–ditto–	–ditto–	(8)	0.92	(88)
3–2		–ditto–	–ditto–	–ditto–	18	(12)	0.74	(70)

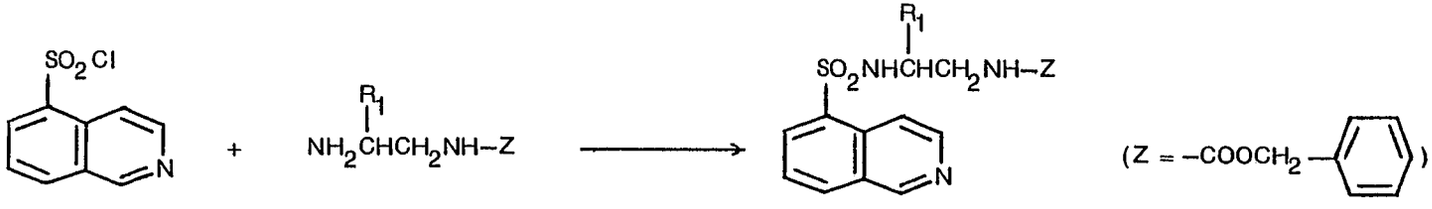
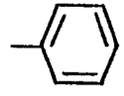


TABLE 8-3

Run No.	Compound No.	R_1	Mass Spectrum (m/e)	IR Absorption Spectrum cap (ν max, cm^{-1})	NMR Spectrum ($CDCl_3$)
1	(7)	C_2H_5	279, 249, 221 192, 128	3400, 2900, 1460 1360, 1160, 1140	0.8(3H, CH_3), 1.0~1.7(2H) 1.9(2H, NH_2), 2.5~4.0(3H) 6.7(1H), 7.6~8.8(5H) 9.3(1H)
2	(8)	n-C_4H_9	307, 277, 221 192, 128	3350, 2900, 1370 1160, 1130	0.7~2.0(9H), 2.1(2H, NH_2) 2.5~3.8(3H), 7.0(1H) 7.6~8.8(5H), 9.3(1H)
3	(12)		327, 297, 192 128	3350, 1610, 1350 1160, 1140	1.7(2H, NH_2), 2.5~4.4(3H) 6.6(1H), 7.1(5H) 7.6~8.8(5H), 9.3(1H)

Example 15

In 50 ml of chloroform were dissolved 2.0 g of 2-acetamidopropylamine and 2.6 g of triethylamine, and to the solution was added dropwise 50 ml of a chloroform solution containing 3.28 g of 5-isoquinolinesulfonyl chloride under cooling with ice. Then the mixed solution was stirred at a temperature of 15°C to 25°C for two hours, and the reaction solution was washed with water, dried with anhydrous magnesium sulfate and the chloroform was distilled therefrom under reduced pressure to give 3.67 g of N-(2-acetamidopropyl)-5-isoquinolinesulfonamide in a yield of 83%.

NMR spectrum ($CDCl_3$): 1.0 (3H, d, CH_3), 2.2 (3H, $COCH_3$), 2.6—3.8 (3H), 5.5—7.0 (2H), 7.6 (1H), 8.0—8.7 (4H) and 9.3 (1H)

IR absorption spectrum ($\nu_{max.}^{cap}$, cm^{-1}): 3300, 1670, 1365, 1150, 1130.

The reaction mixture of 3.0 g of the N-(2-acetamidopropyl)-5-isoquinolinesulfonamide as obtained above and 50 ml of 10% hydrochloric acid was stirred at a temperature of 90°C to 100°C for 36 hours. Then the reaction solution was washed with chloroform, rendered alkaline with 1N sodium hydroxide and extracted with chloroform. The chloroform layer was washed with water, dried with anhydrous magnesium sulfate, and the chloroform was distilled therefrom under reduced pressure. The residue thus obtained was subjected to an alumina column chromatography (alumina: 70 g; solvent: chloroform) to give 1.14 g of N-(2-aminopropyl)-5-isoquinolinesulfonamide, i.e., Compound (9) in a yield of 44%.

Mass spectrum (m/e): 265, 222, 193, 129 and 128

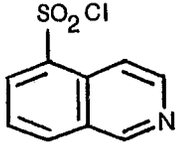
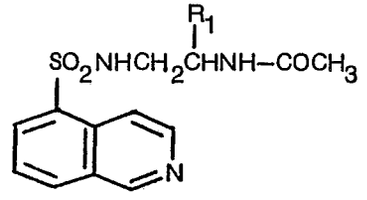
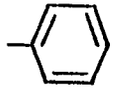
NMR spectrum ($CDCl_3$): 1.0 (3H), 1.7 (2H), 2.9—4.0 (3H), 6.8 (1H), 7.5 (1H), 8.1—8.6 (4H) and 9.3 (1H)

IR absorption spectrum ($\nu_{max.}^{cap}$, cm^{-1}): 3400, 1610, 1460, 1370, 1150 and 1130.

The same procedures as described above were repeated using the compounds of Formula (IV) as set forth in Table 9—1 under the reaction conditions as set forth in Table 9—1 and Table 9—2, and there were obtained N-(2-amino-3-methylbutyl)-5-isoquinolinesulfonamide, i.e., Compound (11) and N-(2-amino-2-phenylethyl)-5-isoquinolinesulfonamide, i.e., Compound (13).

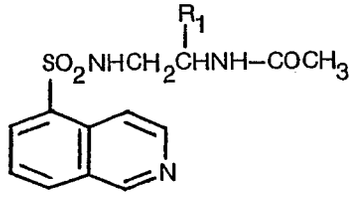
The analytical values of these compounds are shown in Table 9—3.

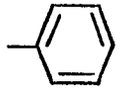
TABLE 9-1

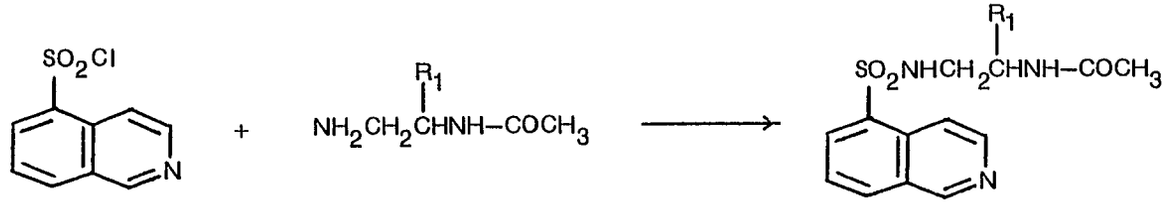
Run No.	 (g)	R_1	(g)	$N(C_2H_5)_3$ (g)	Reaction Temperature (°C)	Reaction Time (hour)	 Yield [g	(%)]	IR Absorption Spectrum (ν cap max, cm^{-1})
1-1	2.28	i-C_3H_7	2.16	1.6	15 ~ 20	0.5	2.31	(69)	1665, 1330, 1160
2-1	-ditto-		2.67	-ditto-	-ditto-	1	2.77	(75)	1660, 1330, 1160

0 061 673

TABLE 9-2

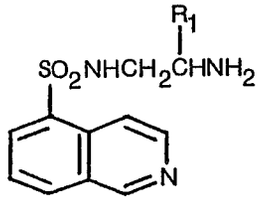


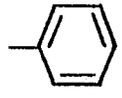
Run No.	R_1	(g)	10% HCl (ml)	Reaction Temperature (°C)	Reaction Time (hour)	Product Compound No.	Yield [g	(%)]
1-2	i-C_3H_7	1.34	30	100	35	(11)	0.60	(51)
2-2		1.11	-ditto-	-ditto-	30	(13)	0.38	(39)



0 061 673

TABLE 9-3

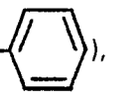


Run No.	Compound No.	R_1	Mass Spectrum (m/e)	IR Absorption Spectrum (ν_{max}^{cap}, cm^{-1})	NMR Spectrum ($CDCl_3$)
1	(11)	i-C_3H_7	221, 192, 148 128	3450, 1600, 1460 1330, 1160, 1140	0.9(6H, 2xCH_3), 1~1.8(1H) 2.5~3.8(3H), 2.1(2H) 7.6(1H), 8.1~8.9(4H) 9.3(1H)
2	(13)		221, 192, 148 128	3400, 1610, 1440 1400, 1330, 1150	1.7(2H, NH_2), 2.7~4.0(3H) 6.8(1H), 7.2(5H), 7.6(1H) 8.0~8.8(4H), 9.3(1H)

Example 16

In 70 ml of methylene chloride were dissolved 3.24 g of 2-(2-N-methyl-N-benzylamino)ethylamine and 2.0 g of triethylamine, and to the solution was added dropwise 50 ml of a methylene chloride solution containing 3.0 g of 5-isoquinolinesulfonyl chloride under cooling with ice. After the dropwise addition of the methylene chloride solution, the mixed solution was stirred at a temperature of 15°C to 25°C for one hour, and then the reaction solution was washed with water and extracted with a 10% aqueous hydrochloric acid solution. The aqueous layer was washed with chloroform, rendered alkaline with a 1N aqueous sodium hydroxide solution, extracted with chloroform, and then the chloroform layer was washed with water, dried with anhydrous magnesium sulfate and the chloroform was distilled therefrom under reduced pressure. The residue thus obtained was subjected to a silica gel column chromatography (silica gel: 100 g; solvent: chloroform) to give 3.84 g of N-[2-(N-methyl-N-benzylamino)ethyl]-5-isoquinolinesulfonamide, i.e. Compound (65) in a yield of 84%.

Mass spectrum (m/e): 355, 340, 264, 221 and 128

NMR spectrum ($CDCl_3$): 1.9 (3H, NCH_3), 2.3—2.7 (2H), 3.0—3.3 (2H), 3.5 (2H, CH_2— ), 6.8 (1H), 7.2 (5H), 7.6 (1H), 8.0—8.5 (4H) and 9.3 (1H)

IR absorption spectrum ($\nu_{max.}^{cap}$, cm^{-1}): 3050, 2950, 1620, 1450, 1330, 1155 and 1135.

The same procedures as described above were repeated using the compound of Formula (III) as set forth in Table 10—1 under the reaction conditions as set forth in Table 10—1, and there was obtained N-[2-(N-isopropyl-N-benzylamino)ethyl]-5-isoquinolinesulfonamide, i.e., Compound (67). The analytical values of this compound are shown in Table 10—2.

TABLE 10-1

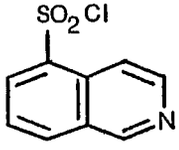
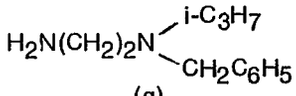
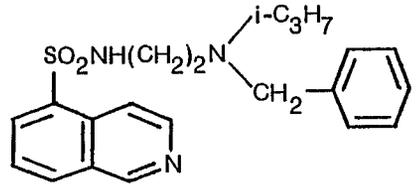
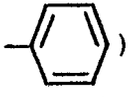
 (g)	$H_2N(CH_2)_2N$  (g)	$N(C_2H_5)_3$ (g)	Reaction Temperature (°C)	Reaction Time (hour)	Product Compound (67) Yield [g	(%)]
4.55	3.84	2.2	15 ~ 25	1	5.44	(71)

TABLE 10-2

Product Compound (67)	Mass Spectrum (m/e)	IR Absorption Spectrum cap (ν max, cm^{-1})	NMR Spectrum ($CDCl_3$)
	383, 340 221, 128	2950, 1610, 1450 1335, 1160, 1140	0.9(6H, 2xCH_3), 2.5~2.8(3H) 3.3(2H), 3.7(2H, CH_2 ) 6.8(1H), 7.2(5H), 7.6~8.5(5H) 9.3(1H)

Example 17

In 100 ml of ethanol was dissolved 2.0 g of N-[2-(N-methyl-N-benzylamino)ethyl]-5-isoquinolinesulfonamide, i.e., Compound (65) as obtained in Example 16, and to the solution was added 0.2 g of 10% palladium-carbon. Then the solution was vigorously stirred at a temperature of 20°C to 25°C in a hydrogen stream of 2.0 to 2.5 atm. for 5 hours. After the palladium-carbon was separated from the reaction solution by filtration, the reaction solution was concentrated to dryness to give 0.95 g of N-(2-methylaminoethyl)-5-isoquinolinesulfonamide, i.e., Compound (14) in a yield of 64%.

Mass spectrum (m/e): 265, 250, 221 and 128

NMR spectrum ($CDCl_3$): 1.7 (1H, N*H*), 2.9 (3H, C*H*$_3$), 2.5—3.1 (2H), 3.1—3.5 (2H), 7.0 (1H), 7.6 (1H), 8.1—8.5 (4H) and 9.3 (1H)

IR absorption spectrum ($\nu_{max.}^{cap}$, cm^{-1}): 3400, 1610, 1350, 1330, 1160 and 1140.

The same procedures as described above were repeated using Compound (67) under the reaction conditions as set forth in Table 11—1, and there was obtained N-(2-isopropylaminoethyl)-5-isoquinolinesulfonamide, i.e., Compound (16). The analytical values of this compound are shown in Table 11—2.

TABLE 11-1

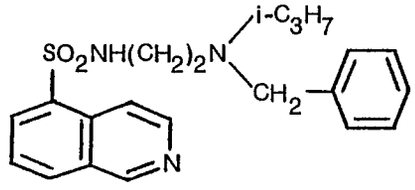
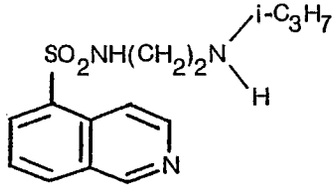
Starting Material (g)	10% Pd-C (g)	Hydrogen Pressure (atm.)	Reaction Temperature (°C)	Reaction Time (hour)	Product Yield [g (%)]
 Compound (67)	0.15	2	20 ~ 25	10	0.50 (44)

TABLE 11-2

Product Compound (16)	Mass Spectrum (m/e)	IR Absorption Spectrum (ν_{max}^{cap}, cm^{-1})	NMR Spectrum ($CDCl_3$)
	293, 263, 221 143, 128	3400, 1600, 1350, 1330 1160, 1140	1.0(6H, 2xCH_3), 2.1(1H, NH) 2.5~2.9(2H), 3.0~3.5(3H) 6.8(1H), 7.6~8.8(5H), 9.3(1H)

Relaxation of Mesenteric Artery

After a home bred rabbit of a Japanese species weighing about 3 Kg was subjected to bloodletting, resulting in death and then to abdominal incision, the mesenteric artery was taken out, cut into helicoids of 2 mm x 25 mm and suspended in a 20 ml organ bath filled with a Krebs-Henseleit solution into which a mixed gas of 95% by volume of O_2 and 5% by volume of CO_2 was introduced and one end of the artery was connected with an isometric transducer. When a load of 1.5 g was applied to the artery, the contraction and the relaxation of the artery were recorded as a weight on the transducer (a product of Nippon Koden K.K., Japan, "FD Pickup TB—912T"). The relaxation of the mesenteric artery was observed by adding the isoquinolinesulfonyl derivatives and their pharmaceutically acceptable acid addition salts of this invention to the mesenteric artery at the condition of about one half of the maximum contraction with KCl at KCl concentration of 15—20 mM. When the complete relaxation of the mesenteric artery was designated 100%, the concentration of the isoquinolinesulfonyl derivatives and their pharmaceutically acceptable acid addition salts which brought about a relaxation of 50% is shown in Table 12.

TABLE 12

Compound Nos.	Relaxation of Mesenteric Artery ED_{50} (μM)	Compound Nos.	Relaxation of Mesenteric Artery ED_{50} (μM)
(1)	5	(9)	15
(2)	7	(11)	28
(3)	11	(12)	18
(4)	10	(13)	25
(5)	14	(14)	12
(6)	10	(16)	10
(7)	21	(17)	10
(8)	19	(18)	30
(19)	17	(42)	18
(20)	42	(43)	6.1
(21)	50	(44)	8.6
(22)	42	(45)	7.5
(23)	4.0	(46)	6.5
(24)	17	(47)	24
(25)	13	(48)	1.8
(26)	8.8	(49)	10
(27)	21	(50)	16
(28)	19	(51)	19
(29)	13	(53)	7
(30)	8.9	(54)	11
(31)	28	(55)	9
(32)	16	(56)	23
(33)	11	(57)	12
(34)	10	(58)	40
(35)	0.6	(59)	6.8
(36)	7.7	(60)	27
(37)	4.0	(61)	24
(38)	5.0	(63)	13
(39)	9.5	(65)	13
(40)	0.6	(67)	18
(41)	1.5		

Effect on Blood Flow Volume of Femoral and Vertebral Arteries of Dog

The effect on the vasodilatation of the femoral and vertebral arteries was measured by anesthetizing a dog of mixed breed weighing 8 to 15 Kg by an intravenous administration of 35 mg/Kg of pentbarbital, providing an acute type probe (a product of Nippon Koden K.K., Japan) with the femoral and vertebral arteries, administering the 5-isoquinolinesulfonyl derivatives and their pharmaceutically acceptable acid addition salts to the femoral vein through a polyethylene tube inserted into the femoral vein side chain and measuring the blood flow volume with an electromagnetic blood flowmeter (a product of Nippon Koden K.K., Japan, "MF-27"). The results are shown in Table 13.

TABLE 13

Compound No.	Amount of Intravenous Administration (mg/Kg)	Increased Blood Flow Volume in Femoral Artery (%)	Increased Blood Flow Volume in Vertebral Artery (%)
1	1	30	45
3	1	33	36
19	1	25	20
25	1	38	29
33	1	35	37
35	1	69	98
36	1	35	63
37	1	65	90
40	1	50	110
46	1	32	55
51	1	39	68
59	1	25	49

Acute Toxicity

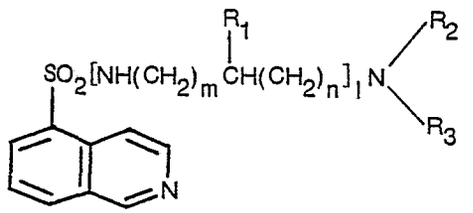
The acute toxicity of the 5-isoquinolinesulfonyl derivatives and their pharmaceutically acceptable acid addition salts was measured by giving male ddY-strain mice an intravenous administration. The results are shown in Table 14.

TABLE 14

Compound Nos.	LD_{50} (mg/Kg)
1	108
3	87
19	180
25	137
33	150
35	29
36	94
37	89
40	42
46	130
51	108
59	145

Claims

1. A compound of Formula (I):



(I)

wherein

l is zero or one;

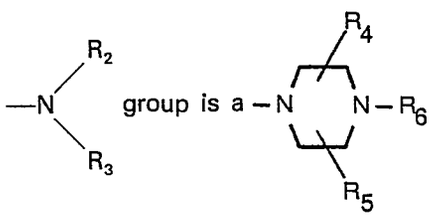
m and n each is zero or an integer of one to nine;

m+n is an integer of at least one;

R_2 is a hydrogen atom, a C_{1-10} alkyl group or a phenyl group;

R_2 and R_3 each is a hydrogen atom, a C_{1-10} alkyl group, a C_{5-6} cycloalkyl group, a phenyl group or a benzyl group; or

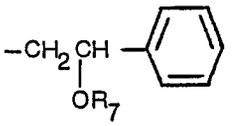
R_2 and R_3 are C_{1-6} alkylene groups and linked directly or through an oxygen atom to form a 5- to 7-membered heterocyclic ring with the adjacent nitrogen atom; or the



group wherein

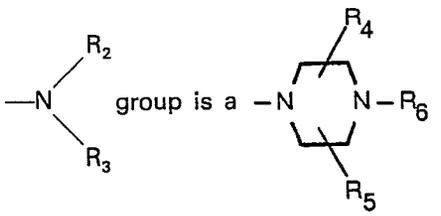
R_4 and R_5 each is a hydrogen atom, a C_{1-10} alkyl group, a phenyl group or a benzyl or phenethyl group and

R_6 is a hydrogen atom, a C_{1-10} alkyl group, a phenyl group, a benzyl or phenethyl group, a benzoyl group, a cinnamyl group, a cinnamoyl group, a furoyl group or a

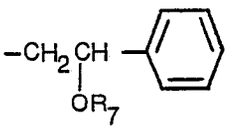


group wherein R_7 is a C_{1-8} alkyl group;
and the pharmaceutically acceptable acid addition salt thereof.

2. The compound of claim 1 wherein l is zero; R_2 and R_3 each is a hydrogen atom, a C_{1-8} alkyl group, a phenyl group or a benzyl group and when one of R_2 and R_3 is a hydrogen atom, the other is not a hydrogen atom; or R_2 and R_3 are C_{1-6} alkylene groups and linked directly or through an oxygen atom to form a 5- to 7-membered heterocyclic ring together with the adjacent nitrogen atom; or the



group wherein R_4 and R_5 each is a hydrogen atom, a C_{1-6} alkyl group, a phenyl group, an α-phenethyl group, a β-phenethyl group or a benzyl group and R_6 is a hydrogen atom, a C_{1-6} alkyl group, a phenyl group, a benzyl group, a phenethyl group, a benzoyl group, a cinnamyl group, a cinnamoyl group, a furoyl group or a

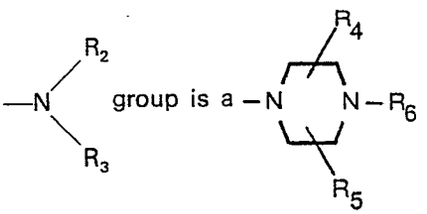


group wherein R_7 is a C_{1-4} alkyl group.

3. The compound of claim 2 wherein R_2 is a hydrogen atom or a C_{1-6} alkyl group and R_3 is a C_{1-6} alkyl group.

4. The compound of claim 2 wherein R_2 and R_3 form together with the adjacent nitrogen atom a 1-pyrrolidinyl group, a piperidino group or a morpholino group.

5. The compound of claim 2 wherein the

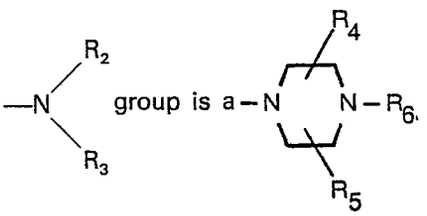


group wherein R_6 is a hydrogen atom and R_4 and R_5 each is a hydrogen atom, a C_{1-6} alkyl group, a phenyl group or a benzyl group.

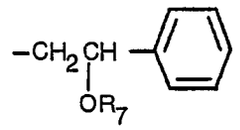
6. The compound of claim 5 wherein R_6, R_4 and R_5 are hydrogen atoms.

7. The compound of claim 5 wherein R_6 is a hydrogen atom, R_4 is a hydrogen atom or a C_{1-6} alkyl group and R_5 is a C_{1-6} alkyl group, a phenyl group or a benzyl group.

8. The compound of claim 2 wherein the

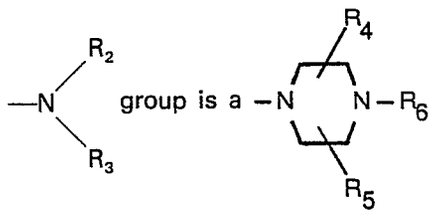


group wherein R_4 and R_5 are hydrogen atoms and R_6 is a C_{1-6} alkyl group, a phenyl group, a benzyl group, a phenethyl group, a benzoyl group, a cinnamyl group, a cinnamoyl group, a furoyl group or a

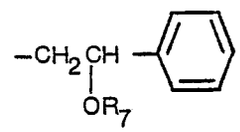


group wherein R_7 is a C_{1-4} alkyl group.

9. The compound of claim 1 wherein l is one; m and n each is zero or an integer of one to nine; m+n is an integer of one to nine; R_1 is a hydrogen atom, a C_{1-6} alkyl or a phenyl group; R_2 and R_3 each is a hydrogen atom, C_{1-8} alkyl group, a C_{5-6} cycloalkyl group, a phenyl group or a benzyl group; or R_2 and R_3 are C_{1-6} alkylene groups and linked directly or through an oxygen atom to form a 5- to 7-membered heterocyclic ring together with the adjacent nitrogen atom; or the



group wherein R_4 and R_5 each is a hydrogen atom, a C_{1-6} alkyl group, a phenyl group or a benzyl group and R_6 is a hydrogen atom, a C_{1-6} alkyl group, a phenyl group, a benzyl group, a phenethyl group, a benzoyl group, a cinnamyl group, a cinnamoyl group, a furoyl group or a



group wherein R_7 is a C_{1-4} alkyl group.

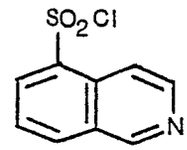
10. A compound of claim 9 wherein m and n each is zero or an integer of one to nine; m+n is an integer of one to nine; and R_1, R_2 and R_3 are hydrogen atoms.

11. The compound of claim 9 wherein m and n each is zero or one; m+n is one; R_1 is a C_{1-6} alkyl group or a phenyl group; and R_2 and R_3 are hydrogen atoms.

12. The compound of claim 9 wherein m and n each is zero or an integer of one to two; m+n is one or two; R_1 is a hydrogen atom; R_2 is a hydrogen atom or a C_{1-4} alkyl group; and R_3 is a C_{1-6} alkyl group, a C_{5-6} cycloalkyl group, a phenyl group or a benzyl group.

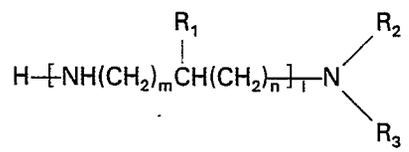
13. The compound of claim 9 wherein m and n each is zero or an integer of one to two; m+n is one or two; and R_2 and R_3 form together with the adjacent nitrogen atom a piperidino group or a morpholino group.

14. A process of preparing the compound of Formula (I) of claim 1 which comprises reacting 5-isoquinolinesulfonyl chloride of Formula (II)



(II)

with a compound of Formula (III)



(III)

wherein

l is zero or one;

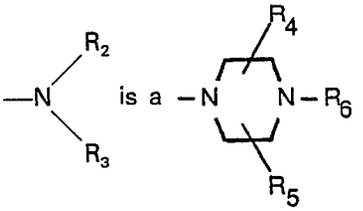
m and n each is zero or an integer of one to nine;

m+n is an integer of at least one;

R_1 is a hydrogen atom, a C_{1-10} alkyl group or a phenyl group;

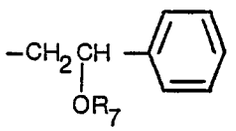
R_2 and R_3 each is a hydrogen atom, a C_{1-10} alkyl group, a C_{5-6} cycloalkyl group, a phenyl group or a benzyl group; or

R_2 and R_3 are C_{1-6} alkylene groups and linked directly or through an oxygen atom to form a 5- to 7-membered heterocyclic ring together with the adjacent nitrogen atom; or the



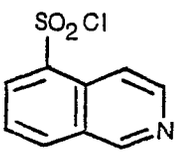
group wherein R_4 and R_5 each is a hydrogen atom, a C_{1-10} alkyl group, a phenyl group or a benzyl or phenethyl group and

R_6 is a hydrogen atom, a C_{1-10} alkyl group, a phenyl group, a benzyl or phenethyl group, a benzoyl group, a cinnamyl group, a cinnamoyl group, a furoyl group or a



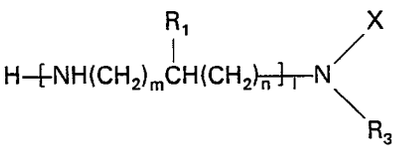
group wherein R_7 is a C_{1-8} alkyl group.

15. A process of preparing the compound of Formula (I) of claim 1 wherein R_2 is a hydrogen atom which comprises reacting 5-isoquinolinesulfonyl chloride of Formula (II)



(II)

with a compound of Formula (IV)



(IV)

wherein

l is zero or one;

m and n each is zero or an integer of one to nine;

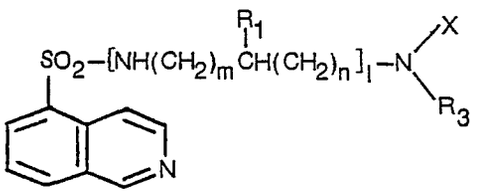
m+n is an integer of at least one;

R_1 is a hydrogen atom, a C_{1-10} alkyl group or a phenyl group;

R_3 is a hydrogen atom, a C_{1-10} alkyl group, a C_{5-6} cycloalkyl group, a phenyl group or a benzyl group; and

X is a protective group,

to give a compound of Formula (V)

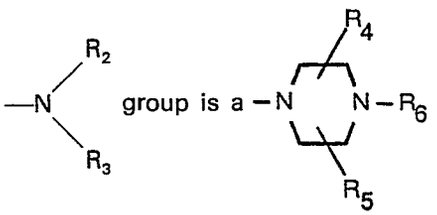


(V)

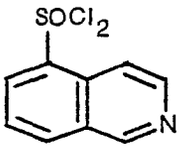
wherein

l, m, n, R_1, R_3 and X are the same as defined above, and eliminating the protective group from the compound of Formula (V).

16. A process of preparing the compound of Formula (I) of claim 1 wherein I is zero and the

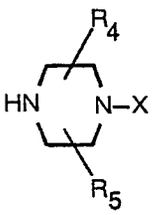


group wherein R_6 is a hydrogen atom which comprises reacting 5-isoquinolinesulfonyl chloride of Formula (II)



(II)

with a compound of Formula (VII)



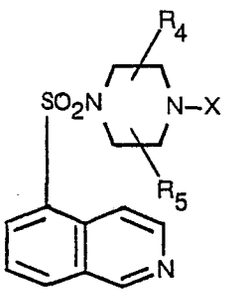
(VII)

wherein

R_4 and R_5 each is a hydrogen atom, a C_{1-10} alkyl group, a phenyl group or a benzyl or phenethyl group; and

X is a protective group,

to give a compound of Formula (VIII)

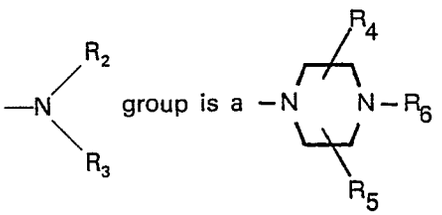


(VIII)

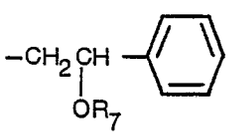
and eliminating the protective group from the compound of Formula (VIII).

17. The process according to any of the preceding claims, wherein the protective group is a formyl, acetyl, benzoyl, arylmethyloxycarbonyl, alkyloxycarbonyl or benzyl group.

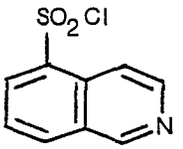
18. A process of preparing the compound of Formula (I) of claim 1 wherein I is zero and the



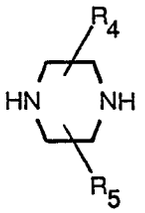
wherein R_6 is a C_{1-10} alkyl group, a phenyl group, a benzyl or phenethyl group, a benzoyl group, a cinnamyl group, a cinnamoyl group, a furoyl group or a



group wherein R_7 is a C_{1-8} alkyl group which comprises reacting 5-isoquinolinesulfonyl chloride of Formula (II)



with a compound of Formula (X)

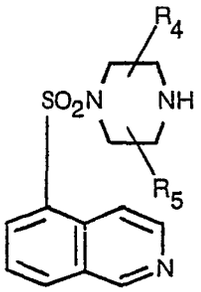


(X)

wherein

R_4 and R_5 each is a hydrogen atom, a C_{1-10} alkyl group, a phenyl group or a benzyl or phenethyl group,

to give a compound of Formula (XI)



(XI)

wherein

R_4 and R_5 are the same as defined above,

and reacting the compound of Formula (XI) with a compound of the formula

$$R_6—W$$

wherein

R_6 is the same as defined above; and

W is an eliminable group.

19. The process of claim 18 wherein the eliminable group is a halogen atom, a substituted sulfonyloxy group or a sulfuric acid residue.

20. The process according to any of the preceding claims, wherein the amount of the compound of Formulae (III), (IV), (VII) and (X) respectively is at least 1 mol per mol of the compound of Formula (II).

21. The process of claim 20, wherein the amount of the compound of Formula (III), (IV), (VII) and (X) respectively is 1 to 20 mols.

22. The process according to any of the preceding claims, wherein the reaction between the compound of Formula (II) and the compound of the Formulae (III), (IV), (VII) and (X) respectively is carried out in the presence of an acid acceptor.

23. The process of claim 22, wherein the acid acceptor is an alkali metal compound or an organic tertiary amine.

24. The process according to any of the preceding claims, wherein the amount of the acid acceptor is 0.5 to about 10 equivalents for each mol of the compound of Formula (III), (IV), (VII) and (X) respectively.

25. The process according to any of the preceding claims, wherein the amount of the compound of Formula (III), (IV), (VII) and (X) respectively is 1 to 5 mols per mol of the compound of Formula (II) when the acid acceptor is present, and is 2 to 10 mols per mol of the compound of Formula (II) when the acid acceptor is absent, under the condition that the amine used does not have a low boiling point.

26. The process according to any of the preceding claims, wherein the reaction between the compound of Formula (II) and the compound of Formulae (III), (IV), (VII) and (X) respectively is carried out in the presence of a reaction medium.

27. The process of claim 26, wherein the reaction medium is a halogenated hydrocarbon, an alkanol, an ether, N,N-dimethylformamide, dimethyl sulfoxide, acetonitrile or water, or mixtures thereof.

28. The process according to any of the preceding claims, wherein the reaction between the

compound of Formula (II) and the compound of Formula (III), (IV), (VII) and (X) respectively is carried out at a temperature of from −30°C to 150°C.

29. The process according to any of the preceding claims, wherein the reaction time is 0.5 to 48 hours at atmospheric pressure.

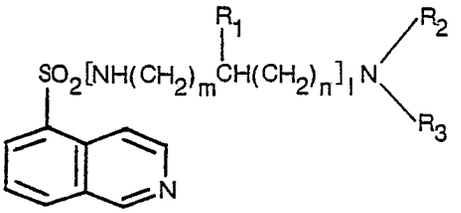
30. The process according to any of the preceding claims, wherein the amount of the compound R_6—W is from 1 mol to 20 mols per mol of the compound of Formula (XI).

31. The process according to any of the preceding claims, wherein the amount of the acid acceptor is 1 to 10 equivalents for each mol of the compound of Formula (III) and (XI) respectively.

32. The process according to any of the preceding claims, wherein the reaction between the compound of Formula (XI) and the compound R_6—W is carried out at a temperature of from −30°C to 200°C.

Patentansprüche

1. Eine Verbindung der Formel (I):



(I)

in der

l null oder eins ist,

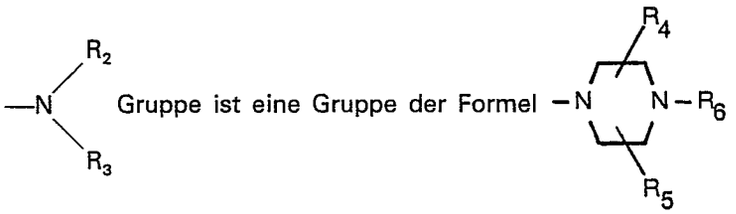
m und n je null oder eine ganze Zahl von eins bis neun bedeuten,

m+n eine ganz Zahl von mindestens eins ist,

R_1 ein Wasserstoffatom, eine C_{1-10}-Alkylgruppe oder eine Phenylgruppe ist,

R_2 und R_3 je ein Wasserstoffatom, eine C_{1-10}-Alkylgruppe, eine C_{5-6}-Cycloalkylgruppe, eine Phenylgruppe oder eine Benzylgruppe sind, oder

R_2 und R_3 C_{1-6}-Alkylengruppen sind, die direkt oder über ein Sauerstoffatom zu einem 5- bis 7-gliedrigen heterocyclischen Ring mit dem benachbarten Stickstoffatom verbunden sind, oder die

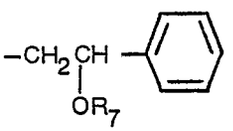


Gruppe ist eine Gruppe der Formel

in der

R_4 und R_5 je ein wasserstoffatom, eine C_{1-10}-Alkylgruppe, eine Phenylgruppe oder eine Benzyl- oder Phenetylgruppe sind und

R_6 ein Wasserstoffatom, eine C_{1-10}-Alkylgruppe, eine Phenylgruppe, eine Benzyl- oder Phenetylgruppe, eine Benzoylgruppe, eine Cinnamylgruppe, eine Cinnamoylgruppe, eine Furoylgruppe oder eine Gruppe der Formel



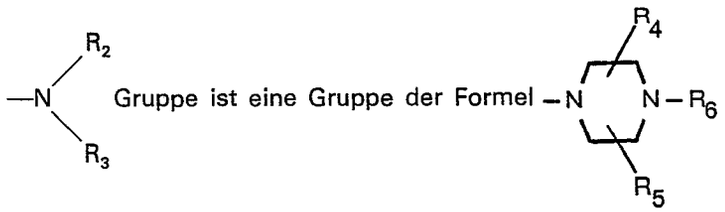
ist,

in der R_7 eine C_{1-8}-Alkylgruppe ist,

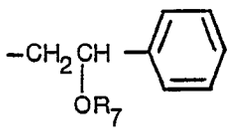
und ihr pharmazeutisch verträgliches Säureadditionssalz.

2. Die Verbindung nach Anspruch 1, in der l null ist, R_2 und R_3 je ein Wasserstoffatom, eine C_{1-8}-Alkylgruppe, eine Phenylgruppe oder eine Benzylgruppe sind und, wenn einer der Reste R_2 und R_3 ein Wasserstoffatom ist, der andere nicht ein Wasserstoffatom ist, oder R_2 und R_3 C_{1-6}-Alkylengruppen, die

direkt oder über eine Sauerstoffatom zu einem 5- bis 7-gliedrigen heterocyclischen Ring mit dem benachbarten Stickstoffatomn verbunden sind, oder die



in der R_4 und R_5 je ein Wasserstoffatom, eine C_{1-6}-Alkylgruppe, eine Phenylgruppe, eine alpha-Phenetylgruppe, eine β-Phenetylgruppe oder eine Benzylgruppe sind und R_6 ein Wasserstoffatom, eine C_{1-6}-Alkylgruppe, eine Phenylgruppe, eine Benzylgruppe, eine Phenetylgruppe, eine Benzoylgruppe, eine Cinnamylgruppe, eine Cinnamoylgruppe, eine Furoylgruppe oder eine Gruppe der Formel

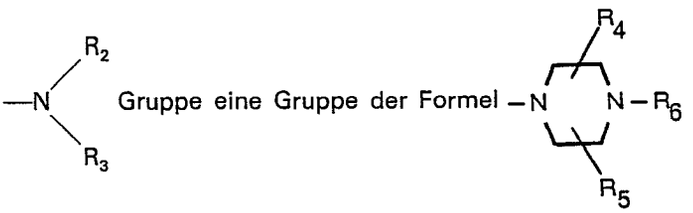


ist, in der R_7 eine C_{1-4}-Alkylgruippe ist.

3. Die Verbindung nach Anspruch 2, in der R_2 ein Wasserstoffatom oder eine C_{1-6}-Alkylgruppe ist und R_3 eine C_{1-6}-Alkylgruppe bedeutet.

4. Die Verbindung nach Anspruch 2, in der R_2 und R_3 zusammen mit dem benachbarten Stickstoffatom eine 1-Pyrrolidinylgruppe, eine Piperidinogruppe oder eine Morpholinogruppe bilden.

5. Die Verbindung nach Anspruch 2, in der die

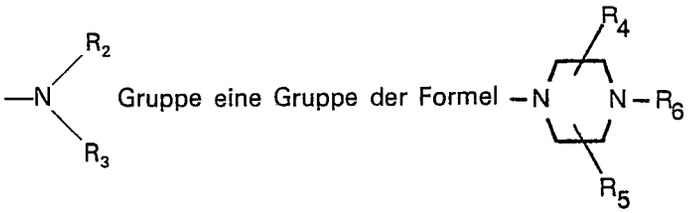


ist, in der R_6 ein Wasserstoffatom ist und R_4 und R_5 je ein Wasserstoffatom, eine C_{1-6}-Alkylgruppe, eine Phenylgruppe oder eine Benzylgruppe sind.

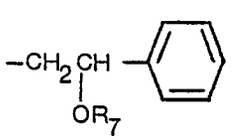
6. Die Verbindung nach Anspruch 5, in der R_6, R_4 und R_5 Wasserstoffatome sind.

7. Die Verbindung nach Anspruch 5, in der R_6 ein Wasserstoffatom ist, R_4 ein Wasserstoffatom oder eine C_{1-6}-Alkylgruppe ist und R_5 eine C_{1-6}-Alkylgruppe, eine Phenylgruppe oder eine Benzylgruppe bedeutet.

8. Die Verbindung nach Anspruch 2, in der die



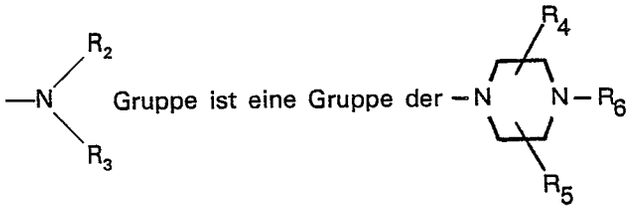
ist, in der R_4 und R_5 Wasserstoffatome sind und R_6 eine C_{1-6}-Alkylgruppe, eine Phenylgruppe, eine Benzylgruppe, eine Phenetylgruppe, eine Benzoylgruppe, eine Cinnamylgruppe, eine Cinnamoylgruppe, eine Furoylgruppe oder eine Gruppe der Formel



ist, in der R_7 eine C_{1-4}-Alkylgruppe ist.

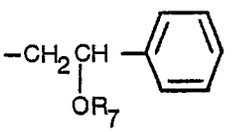
9. Die Verbindung nach Anspruch 1, in der 1 eins ist, m und n je null oder eine ganze Zahl von eins

bis neun bedeuten, m+n eine ganze Zahl von eins bis neun ist, R_1 ein Wasserstoffatom, eine C_{1-6}-Alkyl- oder Phenylgruppe darstellt, R_2 und R_3 je ein Wasserstoffatom, eine C_{1-8}-Alkylgruppe, eine C_{5-6}-Cycloalkylgruppe, eine Phenylgruppe oder eine Benzylgruppe ist, oder R_2 und R_3 sind C_{1-6}-Alkylengruppen, die direkt oder über ein Sauerstoffatom zu einem 5- bis 7-gliedrigen heterocyclischen Ring mit dem benachbarten Stickstoffatom verbunden sind, oder die



Gruppe ist eine Gruppe der

in der R_4 und R_5 je ein Wasserstoffatom, eine C_{1-6}-Alkylgruppe, eine Phenylgruppe oder eine Benzylgruppe sind und R_6 ein Wasserstoffatom, eine C_{1-6}-Alkylgruppe, eine Phenylgruppe, eine Benzylgruppe, eine Phenetylgruppe, eine Benzoylgruppe, eine Cinnamylgruppe, eine Cinnamoylgruppe, eine Furoylgruppe oder eine Gruppe der Formel



ist, in der R_7 eine C_{1-4}-Alkylgruppe ist.

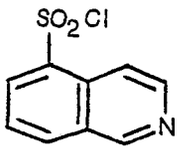
10. Die Verbindung nach Anspruch 9, in der m und n je null oder eine ganze Zahl von eins bis neun bedeuten, m+n eine ganze Zahl von eins bis neun ist und R_1, R_2 und R_3 Wasserstoffatome sind.

11. Die Verbindung nach Anspruch 9, in der m und n je null oder eins bedeuten, m+n eins ist, R_1 eine C_{1-6}-Alkylgruppe oder eine Phenylgruppe ist und R_2 und R_3 Wasserstoffatome sind.

12. Die Verbindung nach Anspruch 9, in der m und n je null oder eine ganze Zahl von eins bis zwei bedeuten, m+n eins oder zwei ist, R_1 ein Wasserstoffatom ist, R_2 ein Wasserstoffatom oder eine C_{1-4}-Alkylgruppe darstellt und R_3 eine C_{1-6}-Alkylgruppe, eine C_{5-6}-Cycloalkylgruppe, eine Phenylgruppe oder eine Benzylgruppe bedeutet.

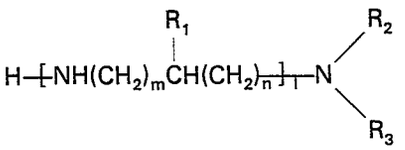
13. Die Verbindung nach Anspruch 9, in der m und n je null oder eine ganze Zahl von eins bis zwei bedeutet, m+n eins oder zwei ist und R_2 und R_3 zusammen mit dem benachbarten Stickstoffatom eine Piperidinogruppe oder eine Morpholinogruppe bilden.

14. Verfahren zur Herstellung der Verbindung der Formel (I) nach Anspruch 1, dadurch gekennzeichnet, daß man 5-Isochinolinsulfonylchlorid der Formel (II)



(II)

mit einer Verbindung der Formel (III) umsetzt



(IV)

in der

l null oder eins ist,

m und n je null oder eine ganze Zahl von eins bis neun bedeuten,

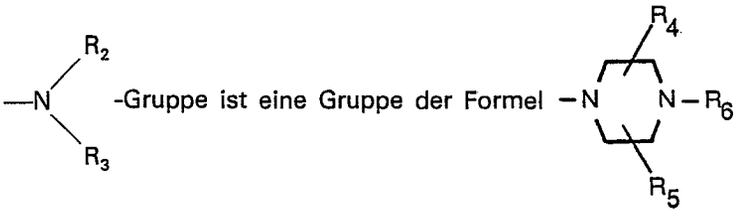
m+n eine ganze Zahl von mindestens eins ist,

R_1 ein Wasserstoffatom, eine C_{1-10}-Alkylgruppe oder eine Phenylgruppe ist,

R_2 und R_3 je ein Wasserstoffatom, eine C_{1-10}-Alkylgruippe, eine C_{5-6}-Cycloalkylgruppe, eine Phenylgruppe oder eine Benzylgruppe bedeuten, oder

R_2 und R_3 C_{1-6}-Alkylengruppen sind, die direkt oder über ein Sauerstoffatom zu einem 5- bis 7-

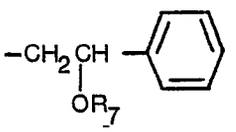
gliedrigen heterocylischen Ring mit dem benachbarten Stickstoffatom verbunden sind, oder die



-Gruppe ist eine Gruppe der Formel

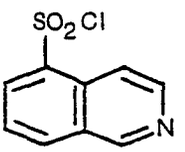
in der R_4 und R_5 je ein Wasserstoffatom, eine C_{1-10}-Alkylgruppe, eine Phenylgruppe, eine Benzyl- oder Phenetylgruppe sind und

R_6 ein Wasserstoffatom, eine C_{1-10}-Alkylgruippe, eine Phenylgruppe, eine Benzyl- oder Phenetylgruppe, eine Benzoylgruppe, eine Cinnamylgruppe, eine Cinnamoylgruppe, eine Furoylgruppe oder eine Gruppe der Formel



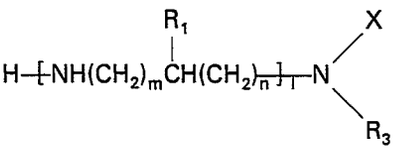
ist, in der R_7 eine C_{1-8}-Alkylgruppe ist.

15. Verfahren zur Herstellung der Verbindung der Formel (I) nach Anspruch 1, in der R_2 ein Wasserstoffatom ist, dadurch gekennzeichnet, daß man 5-Isochinolinsulfonylchlorid der Formel (II)



(II)

mit einer Verbindung der Formel (IV) umsetzt



(IV)

in der

l null oder eins ist,

m und n je null oder eine ganze Zahl von eins bis neun bedeutet,

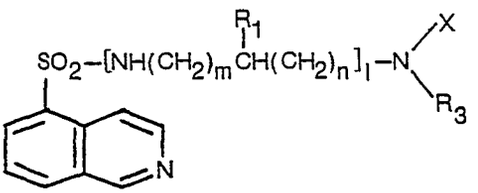
m+n eine ganze Zahl von mindestens eins ist,

R_1 ein Wasserstoffatom, eine C_{1-10}-Alkylgruppe oder eine Phenylgruppe ist,

R_3 ein Wasserstoffatom, eine C_{1-10}-Alkylgruppe, eine C_{5-6}-Cycloalkylgruppe, eine Phenylgruppe oder eine Benzylgruppe darstellt und

X eine Schutzgruppe ist,

zu einer Verbindung der Formel (V)

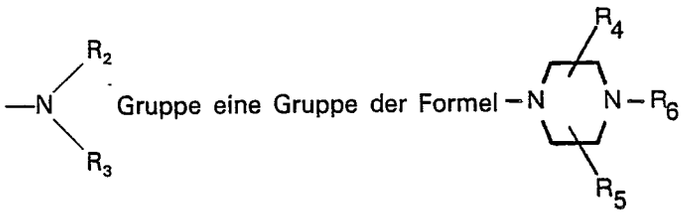


(V)

in der

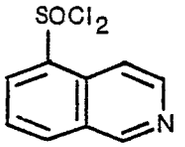
l, m, n, R_1, R_3 und X die gleiche Bedeutung wie oben haben, und die Schutzgruppe aus der Verbindung der Formel (V) entfernt.

16. Ein Verfahren zur Herstellung der Verbindung der Formel (I) nach Anspruch 1, in der 1 null ist und die



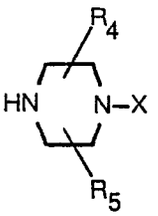
Gruppe eine Gruppe der Formel

ist, in der R_6 ein Wasserstoffatom ist, dadurch gekennzeichnet, daß man 5-Isochinolinsulfonylchlorid der Formel (II)



(II)

mit einer Verbindung der Formel (VII) umsetzt



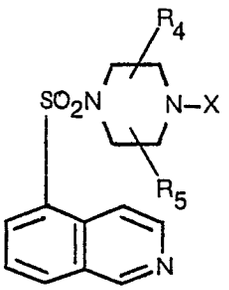
(VII)

in der

R_4 und R_5 je ein Wasserstoffatom, eine C_{1-10}-Alkylgruppe, eine Phenylgruppe oder eine Benzyl- oder Phenetylgruppe sind und

X eine Schutzgruppe ist,

zu einer Verbindung der Formel (VIII)

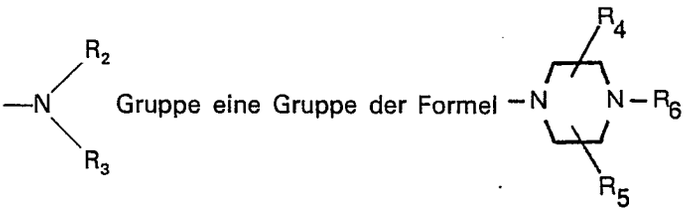


(VIII)

und die Schutzgruppe aus der Verbindung der Formel (VIII) entfernt.

17. Das Verfahren nach einem der vorstehenden Ansprüche, in dem die Schutzgruppe eine Formyl-, Acetyl-, Benzoyl-, Arylmethyloxycarbonyl-, Alkyloxycarbonyl- oder Benzylgruppe ist.

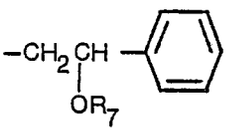
18. Ein Verfahren zur Herstellung der Verbindung der Formel (I) nach Anspruch 1, in der 1 null ist und die



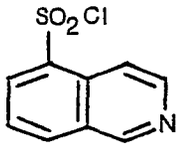
Gruppe eine Gruppe der Formel

ist,

in der R_6 eine C_{1-10}-Alkylgruppe, eine Phenylgruppe, eine Benzyl- oder Phenetylgruppe, eine Benzoylgruppe, eine Cinnamylgruppe, eine Cinnamoylgruppe, eine Furoylgruppe oder eine Gruppe der Formel

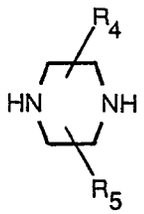


ist, in der R_7 eine C_{1-8}-Alkylgruppe ist, dadurch gekennzeichnet, daß man 5-Isochinolinsulfonylchlorid der Formel (II)



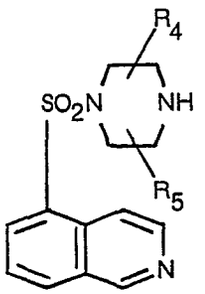
(II)

mit einer Verbindung der Formel (X) umsetzt,



(X)

in der R_4 und R_5 je ein Wasserstoffatom, eine C_{1-10}-Alkylgruppe, eine Phenylgruppe oder eine Benzyl- oder Phenetylgruppe sind,
zu einer Verbindung der Formel (XI)



(XI)

in der
R_4 und R_5 die gleiche Bedeutung haben wie oben,
und die Verbindung der Formel (XI) mit einer Verbindung der Formel

R_6—W umsetzt,

in der R_6 die gleiche Bedeutung wie oben hat, und
W eine abspaltbare Gruppe ist.

19. Das Verfahren nach Anspruch 18, in dem die abspaltbare Gruppe ein Halogenatom, eine substituierte Sulfonyloxygruppe oder ein Schwefelsäurerest ist.

20. Das Verfahren nach einem der vorstehenden Ansprüche, in dem die Menge der Verbindung der Formeln (III), (IV), (VII) bzw. (X) mindestens 1 Mol je Mol der Verbindung der Formel (II) beträgt.

21. Das Verfahren nach Anspruch 20, in dem die Menge der Verbindung der Formel (III), (IV), (VII) bzw. (X) 1 bis 20 Mol beträgt.

22. Das Verfahren nach einem der vorstehenden Ansprüche, in dem die Reaktion zwischen der Verbindung der Formel (II) und der Verbindung der Formeln (III), (IV), (VII) bzw. (X) in Gegenwart eines Säureakzeptors durchgeführt wird.

23. Das Verfahren nach Anspruch 22, in dem der Säureakzeptor eine Alkalimetallverbindung oder ein organisches tertiäres Amin ist.

24. Das Verfahren nach einem der vorstehenden Ansprüche, in dem die Menge des Säureakzeptors, 0,5 bis etwa 10 Äquivalente je Mol der Verbindung der Formel (III), (IV), (VII) bzw. (X) beträgt.

25. Das Verfahren nach einer der vorstehenden Ansprüche, in dem die Menge der Verbindung der Formeln (III), (IV), (VII) bzw. (X) 1 bis 5 Mol je Mol der Verbindung der Formel (II) bei Anwesenheit des Säureakzeptors beträgt und 2 bis 10 Mol je Mol der Verbindung der Formel (II) bei Anwesenheit des Säureakzeptors ist, mit der Bedingung, daß das verwendete Amin keinen niedrigen Siedepunkt hat.

26. Das Verfahren nach einem der vorstehenden Ansprüche, in dem die Reaktion zwischen der Verbindung der Formel (II) und der Verbindung der Formeln (III), (IV), (VII) bzw. (X) in Gegenwart eines Reaktionsmediums durchgeführt wird.

27. Das Verfahren nach Anspruch 26, in dem das Reaktionsmedium ein halogenierter Kohlen-

wasserstoff, ein Alkanol, ein Ether, N,N-Dimethylformamid, Dimethylsulfoxid, Acetonitril oder Wasser oder eines ihrer Gemische ist.

28. Das Verfahren nach einem der vorstehenden Ansprüche, in dem die Reaktion zwischen der Verbindung der Formel (II) und der Verbindung der Formel (III), (IV), (VII) bzw. (X) bei einer Temperatur von −30°C bis 150°C durchgeführt wird.

29. Das Verfahren nach einem der vorstehenden Ansprüche, in dem die Reaktionszeit 0,5 bis 48 h bei Atmosphärendruck beträgt.

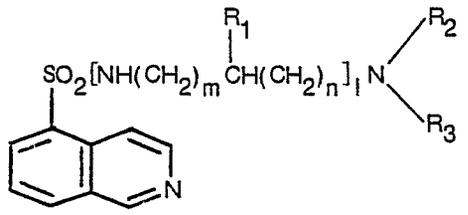
30. Das Verfahren nach einem der vorstehenden Ansprüche, in dem die Menge der Verbindung der Formel R_6—W von 1 Mol bis 20 Mol je Mol der Verbindung der Formel (XI) beträgt.

31. Das Verfahren nach einem der vorstehenden Ansprüche, in dem die Menge des Säureakzeptors 1 bis 10 Äquivalente je Mol der Verbindung der Formeln (III) bzw. (XI) beträgt.

32. Das Verfahren gemäß einem der vorstehenden Ansprüche, in dem die Reaktion zwischen der Verbindung der Formel (XI) und der Verbindung der Formel R_6—W bei einer Temperatur von −30°C bis 200°C durchgeführt wird.

Revendications

1. Composé de formule (I):



(I)

dans laquelle

l est zéro ou un;

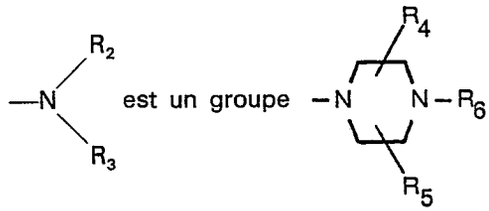
chacun de m et n est zéro ou un nombre entier de 1 à 9;

m+n est un nombre entier d'au moins un;

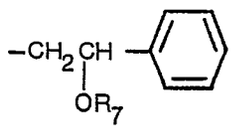
R_1 est un atome d'hydrogène, un groupe alcoyle C_{1-10} ou un groupe phényle;

chacun de R_2 et R_3 est un atome d'hydrogène, un groupe alcoyle C_{1-10}, un groupe cycloalcoyle C_{5-6}, un groupe phényle ou un groupe benzyle; ou

R_2 et R_3 sont des groupes alcoylènes C_{1-6} et liés directement ou par un atome d'oxygène pour former un noyau hétérocyclique à 5 à 7 élements avec l'atome d'azote adjacent; ou le groupe



où chacun de R_4 et R_5 est un atome d'hydrogène, un groupe alcoyle C_{1-10}, un groupe phényle ou un groupe benzyle ou phénéthyle et R_6 est un atome d'hydrogène, un groupe alcoyle C_{1-10}, un groupe phényle, un groupe benzyle ou phénéthyle, un groupe benzoyle, un groupe cinnamyle, un groupe cinnamoyle, un groupe furoyle ou un groupe

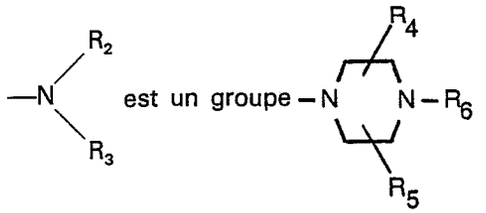


où R_7 est un groupe alcoyle C_{1-8};

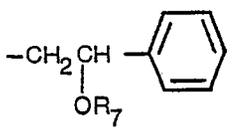
et ses sels d'addition d'acide acceptables en pharmacie.

2. Composée selon la revendication 1, où l est zéro; chacun de R_2 et R_3 est un atome d'hydrogène, un groupe alcoyle C_{1-8}, un groupe phényle ou un groupe benzyle et lorsque l'un de R_2 et R_3 est un atome d'hydrogène, l'autre n'est pas un atome d'hydrogène; ou

R_2 et R_3 sont des groupes alcoylènes C_{1-6} et liés directement ou par un atome d'oxygène pour former un noyau hétérocyclique à 5 à 7 éléments avec l'atome d'azote adjacent; ou bien le groupe



où chacun de R_4 et R_5 est un atome d'hydrogène, un groupe alcoyle C_{1-6}, un groupe phényle, un groupe α-phénéthyle, un groupe β-phénéthyle, ou un groupe benzyle et R_6 est un atome d'hydrogène, un groupe alcoyle C_{1-6}, un groupe phényle, un groupe benzyle, un groupe phénéthyle, un groupe benzoyle, un groupe cinnamyle, un groupe cinnamoyle, un groupe furoyle ou un groupe

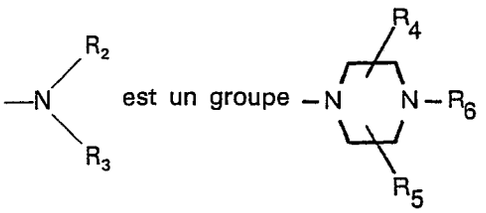


où R_7 est un groupe alcoyle C_{1-4}.

3. Composé selon la revendication 2, où R_2 est un atome d'hydrogène ou un groupe alcoyle C_{1-6} et R_3 est un groupe alcoyle C_{1-6}.

4. Composé selon la revendication 2, où R_2 et R_3 forment ensemble, avec l'atome d'azote adjacent, un groupe 1-pyrrolidinyle, un groupe pipéridino ou un groupe morpholino.

5. Composé selon la revendication 2, où le groupe

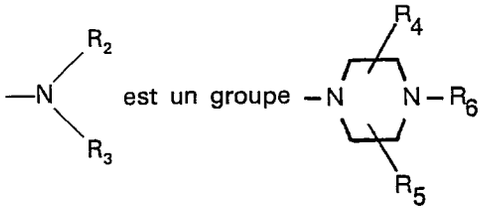


où R_6 est un atome d'hydrogène et chacun de R_4 et R_5 est un atome d'hydrogène, un groupe alcoyle C_{1-6}, un groupe phényle ou un groupe benzyle.

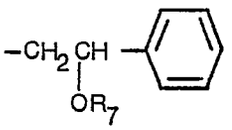
6. Composé selon la revendication 5, où R_6, R_4 et R_5 sont des atomes d'hydrogène.

7. Composé selon la revendication 5, ou R_6 est un atome d'hydrogène, R_4 est un atome d'hydrogène ou un groupe alcoyle C_{1-6} et R_5 est un groupe alcoyle C_{1-6}, un groupe phényle ou un groupe benzyle.

8. Composé selon la revendication 2, où le groupe

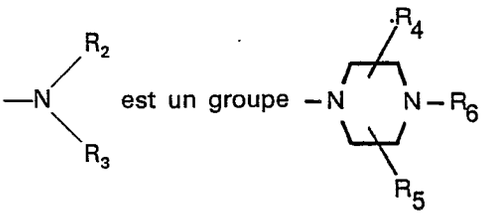


où R_4 et R_5 sont des atomes d'hydrogène et R_6 est un groupe alcoyle C_{1-6}, un groupe phényle, un groupe benzyle, un groupe phénéthyle, un groupe benzoyle, un groupe cinnamyle, un groupe cinnamoyle, un groupe furoyle ou un groupe

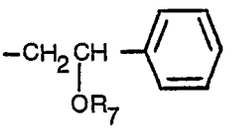


où R_7 est un groupe alcoyle C_{1-4}.

9. Composé selon la revendication 1 ou 1 est 1; chacun de m et n est zéro ou un nombre entier de 1 à 9; m+n est un nombre entier de 1 à 9; R_1 est un atome d'hydrogène; un groupe alcoyle C_{1-6} ou un groupe phényle; chacun de R_2 et R_3 est un atome d'hydrogène, un groupe alcoyle C_{1-8}, un groupe cycloalcoyle C_{5-6}, un groupe phényle ou un groupe benzyle; ou bien R_2 et R_3 sont des groupes alcoylènes C_{1-6} et liés ensemble directement ou par un atome d'oxygène pour former un noyau hétérocyclique à 5 à 7 membres avec l'atome d'azote adjacent ou bien le groupe



où chacun de R_4 et R_5 est un atome d'hydrogène, un groupe alcoyle C_{1-6}, un groupe phényle, ou un groupe benzyle et R_6 est un atome d'hydrogène, un groupe alcoyle C_{1-6}, un groupe phényle, un groupe benzyle, un groupe phénéthyle, un groupe benzoyle, un groupe cinnamyle, un groupe cinnamoyle, un groupe furoyle
ou un groupe



où R_7 est un groupe alcoyle C_{1-4}.

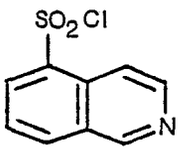
10. Composé selon la revendication 9, où chacun de m et n est zéro ou un nombre entier de 1 à 9; m+n est un nombre entier de 1 à 9; et R_1 et R_3 sont des atomes d'hydrogène.

11. Composé selon la revendication 9, où chacun de m et n est zéro ou 1; n+m est 1; R_1 est un groupe alcoyle C_{1-6} ou un groupe phényle; et R_2 et R_3 sont des atomes d'hydrogène.

12. Composé selon la revendication 9, où chacun de m et n est zéro ou un nombre entier de 1 à 2; m+n est 1 ou 2; R_1 est un atome d'hydrogène; R_2 est un atome d'hydrogène ou un groupe alcoyle C_{1-4}; et R_3 est un groupe alcoyle C_{1-6}, un groupe cycloalcoyle C_{5-6}, un groupe phényle ou un groupe benzyle.

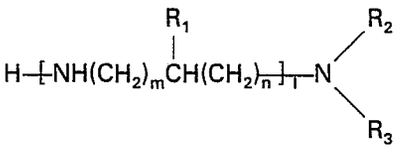
13. Composé selon la revendication 9, où chacun de m et n est zéro ou un nombre entier de 1 à 2; m+n est 1 ou 2; et R_2 et R_3 forment ensemble, avec l'atome d'azote adjacent, un groupe pipéridino ou un groupe morpholino.

14. Procédé de préparation du composé de formule (I) selon la revendication 1 qui consiste á faire réagir du chlorure de 5-isoqinolinesulfonyle de formule (II)



(II)

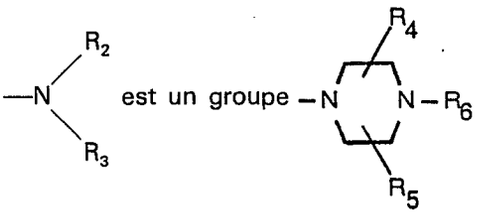
avec un composé de formule (III)



(III)

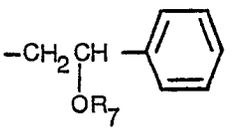
dans laquelle
l est zéro ou un;
chacun de m et n est zéro ou un nombre entier de 1 à 9;
m+n est un nombre entier d'au moins un;
R_1 est un atome d'hydrogène, un groupe alcoyle C_{1-10}, ou un groupe phényle;
chacun de R_2 et R_3 est un atome d'hydrogène, un groupe alcoyle C_{1-10}, un groupe cycloalcoyle C_{5-6}, un groupe phényle ou un groupe benzyle; ou

R_2 et R_3 sont des groupes alcoylènes C_{1-4} et liés directement ou par un atome d'oxygène pour former un noyau hétérocyclique à 5 à 7 éléments avec l'atome d'azote adjacent; ou le



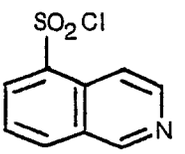
où

chacun de R_4 et R_5 est un atome d'hydrogène, un groupe alcoyle C_{1-10}, un groupe phényle ou un groupe benzyle ou phénéthyle et R_6 est un atome d'hydrogène, un groupe alcoyle C_{1-10}, un groupe phényle, un groupe benzyle ou phénéthyle, un groupe benzoyle, un groupe cinnamyle, un groupe cinnamoyle, un groupe furoyle ou un groupe



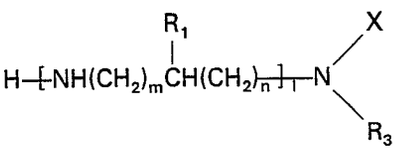
où R_7 est un groupe alcoyle C_{1-8}.

15. Procédé de préparation du composé de formule (I) selon la revendication 1, où R_2 est un atome d'hydrogène qui consiste à faire réagir du chlorure de 5-isoquinolinesulfonyle de formule (II)



(II)

avec un composé de formule (IV)



(IV)

dans laquelle

l est zéro ou un;

chacun de m et n est zéro ou un nombre entier de 1 à 9;

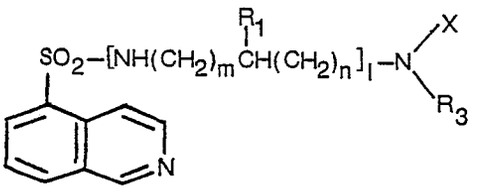
m+n est un nombre entier d'au moins 1;

R_1 est un atome d'hydrogène, un groupe alcoyle C_{1-10}, ou un groupe phényle;

R_3 est un atome d'hydrogène, un groupe alcoyle C_{1-10}, un groupe cycloalcoyle C_{5-6}, un groupe phényle ou un groupe benzyle; et

X est un groupe protecteur,

pour donner un composé de formule (V)

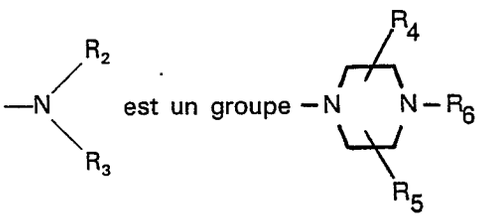


(V)

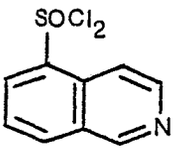
dans laquelle

l, m, n, R_1, R_3 et X sont tels que définis ci-dessus, et à éliminer le groupe protecteur du composé de formule (V).

16. Procédé de préparation du composé de formule (I) selon la revendication 1 où l est zéro et le groupe

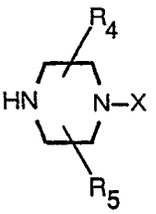


où R_6 est un atome d'hydrogène qui consiste à faire réagir du chlorure de 5-isoquinolinesulfonyle de formule (II)



(II)

avec un composé de formule (VII)



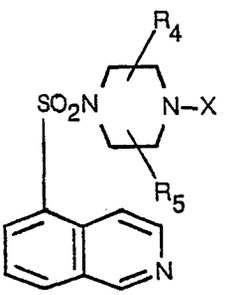
(VII)

dans laquelle

chacun de R_4 et R_5 est un atome d'hydrogène, un groupe alcoyle C_{1-10}, un groupe phényle ou un groupe benzyle ou phénéthyle; et

X est un groupe protecteur,

pour donner un composé de formule (VIII)

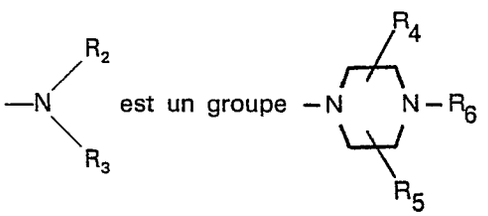


(VIII)

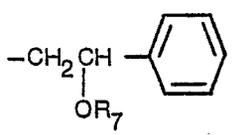
et à éliminer le groupe protecteur du composé de formule (VIII).

17. Procédé selon l'une quelconque des revendications précédentes, où le groupe protecteur est un groupe formyle, acétyle, benzoyle, arylméthyloxycarbonyle, alkyloxycarbonyle ou benzyle.

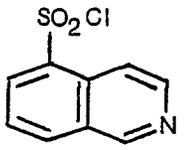
18. Procédé de préparation du composé de formule (I) selon la revendication 1 où l est zéro et le groupe



où R_6 est un groupe alcoyle C_{1-10}, un groupe phényle, un groupe benzyle ou phénéthyle, un groupe benzoyle, un groupe cinnamyle, un groupe cinnamoyle, un groupe furoyle ou un groupe

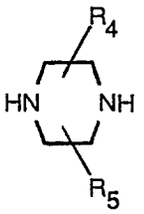


où R_7 est un groupe alcoyle C_{1-8},
qui consiste à faire réagir du chlorure de 5-isoquinolinesulfonyle de formule (II)



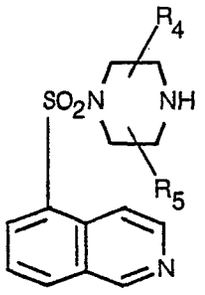
(II)

avec un composé de formule (X)



(X)

dans laquelle
chacun de R_4 et R_5 est un atome d'hydrogène, un groupe alcoyle C_{1-10}, un groupe phényle ou un groupe benzyle ou phénéthyle pour donner un composé de formule (XI)



(XI)

dans laquelle
R_4 et R_5 sont tels que définis ci-dessus, et à faire réagir le composé de formule (XI) avec un composé de formule

$$R_6—W$$

dans laquelle
R_6 est tel que défini ci-dessus; et
W est un groupe éliminable.

19. Procédé selon la revendication 18, où le groupe éliminable est un atome d'halogène, un groupe sulfonyloxy substitué ou un résidu d'acide sulfurique.

20. Procédé selon l'une quelconque des revendications précédentes, où la quantité du composé des formules (III), (IV), (VII) et (X) respectivement est d'au moins 1 mole par mole du composé de formule (II).

21. Procédé selon la revendication 20, caractérisé en ce que la quantité du composé de formule (III), (IV), (VII) et (X) est respectivement d'environ 1 à 20 moles.

22. Procédé selon l'une quelconque des revendications précédentes, où la réaction entre le composé de formule (II) et le composé des formules (III), (IV), (VII) et (X) respectivement est mise en oeuvre en présence d'un accepteur d'acide.

23. Procédé selon la revendication 22, où l'accepteur d'acide est un composé d'un métal alcalin ou une amine tertiaire organique.

24. Procédé selon l'une quelconque des revendications précédentes, où la quantité de l'accepteur d'acide est de 0,5 à environ 10 équivalents, pour chaque mole du composé de formule (III), (IV), (VII) et (X) respectivement.

25. Procédé selon l'une quelconque des revendications précédentes, où la quantité du composé de formule (III), (IV), (VII) et (X) respectivement est de 1 à 5 moles par mole du composé de formule (II) quand l'accepteur d'acide est présent et de 2 à 10 moles par mole du composé de formule (II) quand l'accepteur d'acide est absent, à la condition que l'amine utilisée n'ait pas un faible point d'ébullition.

26. Procédé selon l'une quelconque des revendications précédentes, où la réaction entre le composé de formule (II) et le composé des formules (III), (IV), (VII) et (X) respectivement est mise en oeuvre en présence d'un milieu réactionnel.

27. Procédé selon la revendication 26, où le milieu réactionnel est un hydrocarbure halogéné, un

alcanol, un éther, du N,N-diméthylformamide, du diméthyl sulfoxyde, de l'acétonitrile ou de l'eau ou leurs mélanges.

28. Procédé selon l'une quelconque des revendications précédentes, où la réaction entre le composé de formule (II) et le composé de formule (III), (IV), (VII) et (X) respectivement est mise en oeuvre à une température comprise de —30°C à 150°C.

29. Procédé selon l'une quelconque des revendications précédentes, où la durée de la réaction est d'une demi-heure à 48 heures à la pression atmosphérique.

30. Procédé selon l'une quelconque des revendications précédentes, où la quantité du composé R_6—W est de 1 mole à 20 moles par mole du composé de formule (XI).

31. Procédé selon l'une quelconque des revendications précédentes, où la quantité de l'accepteur d'acide est de 1 à 10 équivalents pour chaque mole du composé de formule (III) et (XI) respectivement.

32. Procédé selon l'une quelconque des revendications précédentes, où la réaction entre le composé de formule (XI) et le composé R_6—W est effectuée à une température de —30°C à 200°C.